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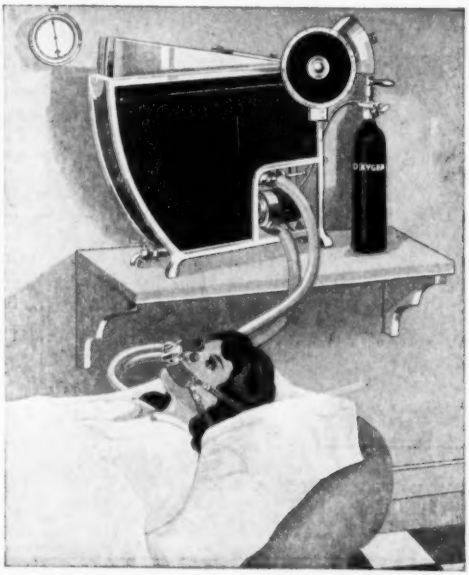

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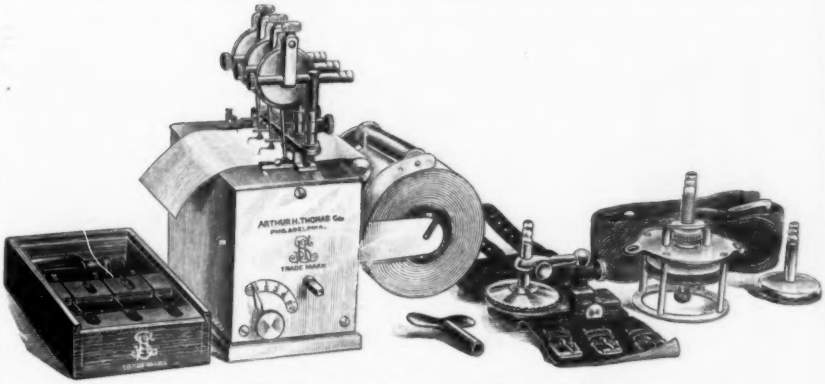

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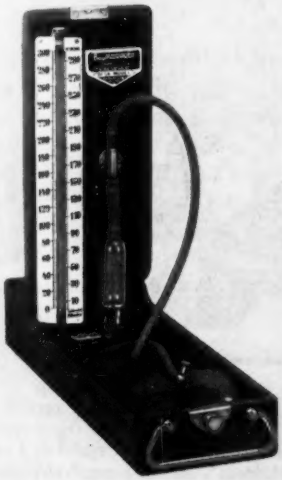

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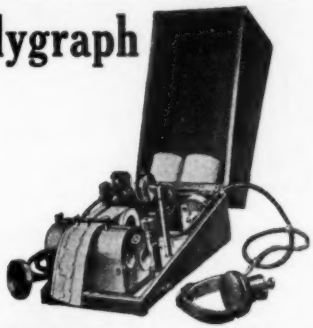

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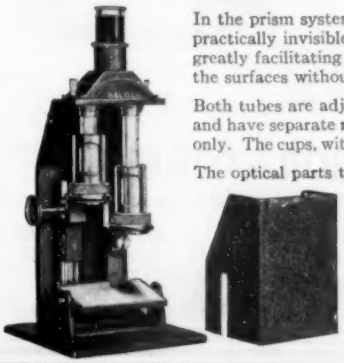

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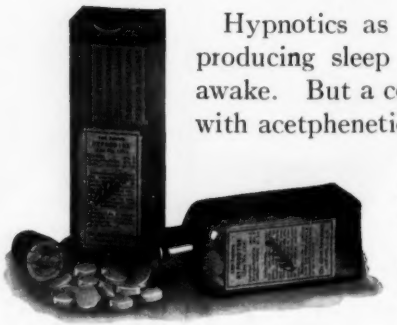

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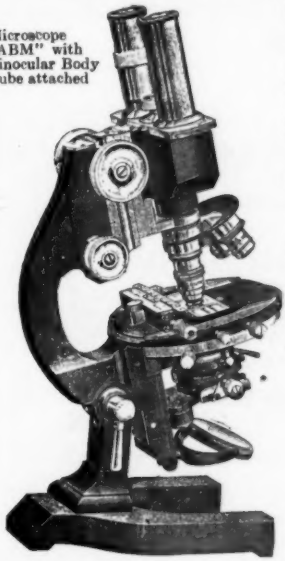

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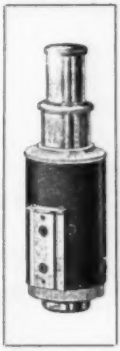

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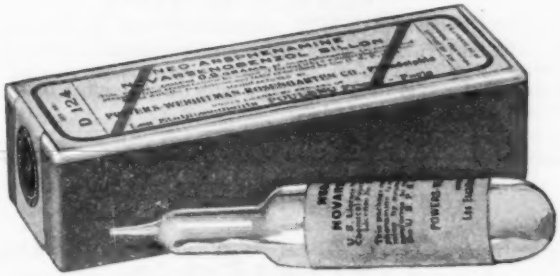

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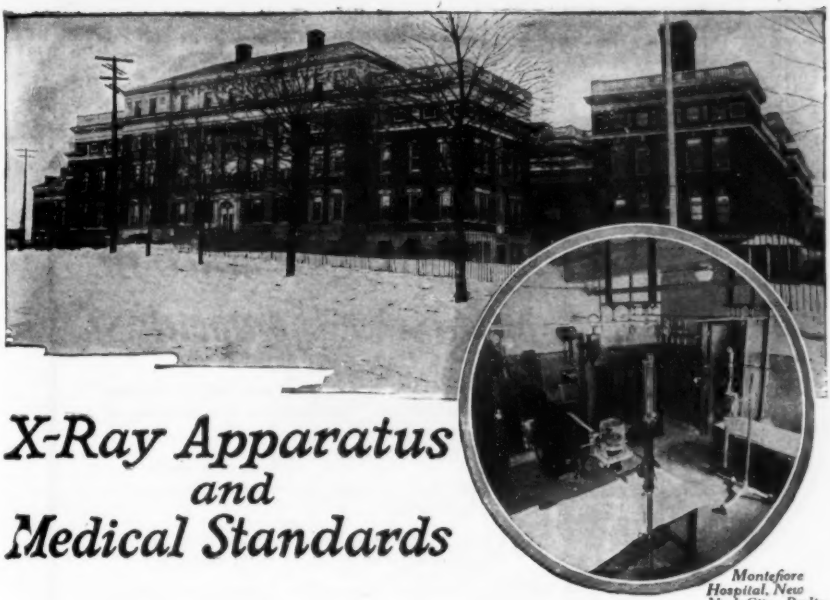

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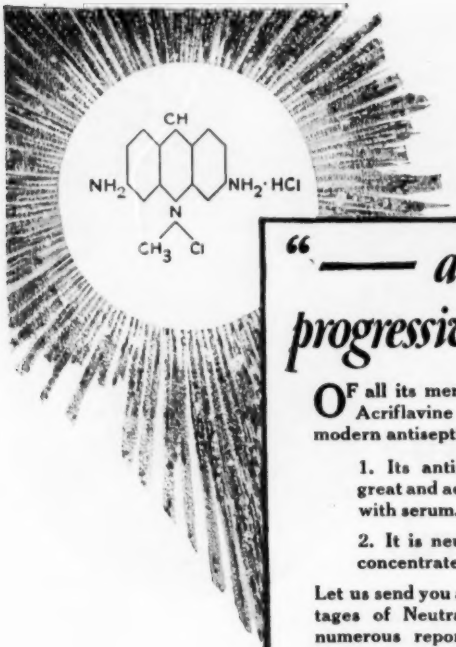

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APRIL, 1923

ORIGINAL ARTICLES.

SOME OBSERVATIONS UPON THE HISTOLOGICAL CHANGES IN LYMPHATIC GLANDS FOLLOWING EXPOSURE TO RADIUM.

By J. C. Mottram, M.D.,

(From the Research Department, Radium Institute, London.)

The following observations were made with reference to certain problems of cancer immunity, although here they are published largely divorced from the cancer problem. They are concerned with the histological changes in the iliac lymphatic gland of the rat which follow exposure of the whole animal to radiations from radium. In this very difficult and controversial field conclusions have only been drawn with great diffidence, and perhaps more especially with a view to encourage other workers to take up what appears to be a profitable line of investigation.

A brief description of the histological structure of the normal iliac lymph gland of the rat is a necessary preliminary. The gland is enclosed in a fine connective tissue capsule, which sends fine processes throughout the gland, dividing it into a sponge-like meshwork. At one or more places a hilum is seen where a thicker band of connective tissue enters the gland, carrying with it bloodvessels and lymphatic vessels. The whole gland is composed of a spongework of lymphatic channels and reticular cells; the afferent lymphatic vessels open into this system at the surface of the gland, the efferent leave it centrally via the hilum. Between these channels lie the various cell masses shown diagrammatically in Fig. 1.

(*a*) Irregular islands of plasmoidocytes occupy the center of the gland; they usually extend to the margin in a few places (X and

Y in Fig. 1). They are grouped around the bloodvessels, and separated by lymphocytic channels, The exact nature of these cells is in doubt; some observers describe them as plasma cells, other consider that they are lymphoid myeloblasts. They closely resemble cells which give rise to red cells in the spleen, and very occasionally have been seen having the same function in the iliac

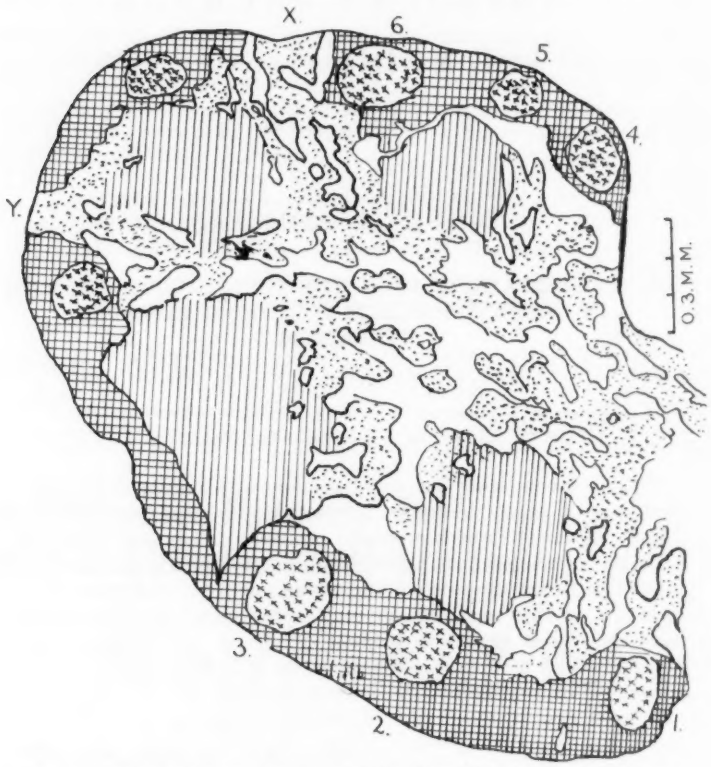

FIG. 1.—Projection drawing of a normal iliac lymphatic gland. Dotted areas, plasmoidocytes; plain areas, lymphatic channels; lined areas, central group of lymphocytes; cross-hatched areas, marginal ring of lymphocytes; areas with crosses, follicles.

lymph gland. As they have not quite typical plasma cell characters, Maximow called them plasmoidocytes, and this term is used throughout this communication.

(*b*) More or less circular masses of lymphocytes are also centrally placed, and grouped around the bloodvessels. They are directly continuous with the plasmoidocyte masses, as shown in Fig. 1

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(lined areas). When they occur the lymphatic channels are collapsed, or filled with lymphocytes.

(*c*) Just within the capsule of the gland there is a ring of lymphocytes (cross hatched areas), quite distinct from the central group of lymphocytes, and not continuous with the plasma cell groups. This ring, as already mentioned, may not be complete; it is absent where the plasma cells reach the margin. It varies considerably in thickness.

(*d*) Round the margin and lying among the marginal lymphocytes are follicles consisting of circular collections of macrophages (clasmatocytes or phagocytic endothelial cells). (Areas with crosses.) Around the outer half of these corpuscles the marginal lymphocytes are especially accumulated, whereas on their inner side they are scanty or absent.

With this general description attention may now be directed to more detailed histological findings. Dividing cells are only to be seen in two situations, among the cells forming the follicles, and among the plasma cells. Mitotic figures, though specially stained for, have never been seen on either the marginal or central groups of lymphocytes.

As regards the follicles, the generally accepted view is that they are the mother cells of the lymphocytes found more or less surrounding them. The following facts are, however, against this conclusion:

1. As before mentioned, the surrounding lymphocytes are numerous toward the outer side, and few or absent on the inner of the follicles: whereas the distribution of the mitotic figures is exactly the reverse (Fig. 2). It follows that cell division is confined to the side where few or no lymphocytes are found.

2. Mitotic figures are not especially confined to the outlying cells of the follicles, and yet lymphocytes are never seen scattered among these cells either in the center of the follicle or toward its inner margin. They are, however, to be seen among the cells forming the outer margin of the follicle, where, however, mitotic figures are very rarely seen.

3. The lymphocytes surrounding the follicles have not the characters of young cells recently divided off. Their protoplasm is not scanty, and the nucleus is irregular in shape, pyknotic, and stains palely. They have, in fact, the characters of old partly degenerated cells rather than young (Fig. 3, *b*).

4. These degenerated appearances are especially marked among the lymphocytes directly abutting on the follicles, and especially among these found scattered among the follicle cells along the outer margin (Fig. 3, *c*).

5. There is evidence that these margin lymphocytes are carried on to the gland by means of the afferent lymphatics. The afferent lymphatics enter the gland all along its outer margin, opening directly into the lymphatic space immediately within the capsule,

and it is clear that any lymphocytes carried in the afferent lymph will be deposited here.

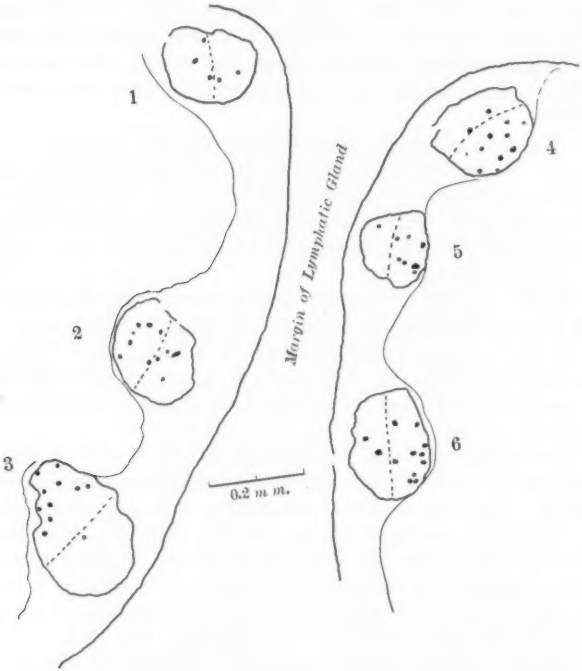

FIG. 2.—The six follicles of Fig. 1, showing the distribution of the mitotic figures. Note that the mitoses are for the most part internal to the middle line (dotted).

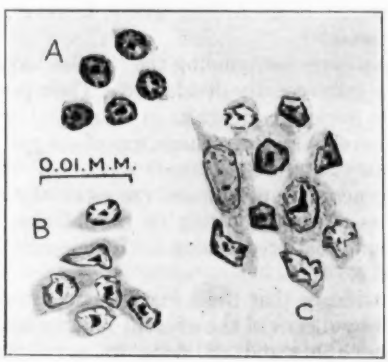

FIG. 3.—Lymphocytes, *a*, from the central group; *b*, from the marginal group; and *c*, lying among the outer cells of the follicles.

To test this the following experiment was carried out. The right iliac glands of six rats were removed. During the succeeding night the animals were subjected to β and γ radiation (unscreened) sufficient to produce a marked disappearance of lymphocytes from the circulation; the left iliac glands were removed the next day, in some cases immediately, and in other cases, a few hours after the radiation was stopped. A histological comparison on the two sets of glands was then made, and it was found that in each case a very great increase in the number of marginal lymphocytes had occurred, without any increase in the number of mitoses in the follicles, and further, that these lymphocytes presented degenerative changes. Control experiments carried out without radiation, using six animals, showed no such change.

If the cells of the follicles do not produce lymphocytes by mitosis they must be converted into some other cells, for their accumulation in the lymphatic gland is limited, and yet their rate of division is rapid, judging from the great number of dividing cells seen. Evidence will be brought forward later as regards their destination.

Nevertheless, they have some relation to the lymphocytes, which accumulate around them in this characteristic manner. The clue to this relationship is given by the numerous cell inclusions to be seen within vacuoles in their protoplasm. They were first described by Flemming, who called them "stainable particles," and concluded that they were particles of chromatin. They stain very deeply with basic dyes, as do dividing and some forms of degenerating chromatin. It is now certain that they represent the phagocytosis of lymphocytes.

The drawing shown in Fig. 4 represents all the stages from the first inclusion of a lymphocyte within the vacuole to its final disintegration into fine granules. The first change is a loss of the structural detail of the nucleus, accompanied by a tendency to stain more darkly than the nuclei of the surrounding, but not yet ingested, lymphocytes. The next change is a fragmentation of the darkened nucleus into at first large, and subsequently small dark granules. Finally these granules gradually change their staining qualities. For instance if stained with pyronin-methyl-green after fixation with acetic alcohol, they first stain purple, but finally the fine granules take only the pyronin, or if stained with eosinate of methylene blue and eosin after fixation with formol-potassium-bichromate, they first stain dark blue, then purple, and finally red. Thus the basic nuclear staining quality gradually changes to a more protoplasmic acid type.

The last stage consists of the disappearance of the vacuole and the disposition of the red granules in the protoplasm chiefly around the surface, away from the nucleus. It is possible that the vacuole may be to some extent due to shrinkage during fixation, as it varies much in size in different specimens.

It may be here mentioned that the amount of this phagocytosis is directly proportional to the number of lymphocytes around the follicles, and it is not seen in the absence of marginal lymphocytes, whereas it is especially abundant with the great marginal accumulation following radiation.

It is doubtful whether all of the marginal lymphocytes are in this way destroyed, or only the more degenerated forms, the others passing through the gland by means of the lymphatic channels and efferent lymphatics.

Turning now to the plasmoidocytes (or myeloblasts) occupying the central areas of the gland, they, like the cells of the follicles, are to be seen undergoing mitosis. It is possible that this division to some extent results in an increase in the number of plasmoidocytes; but such an increase must soon reach a limit, as there is no evidence that these cells leave the gland either in the blood or lymph, or by

FIG. 4.—Follicle cells containing lymphocytes in various stages of phagocytosis.

other means. From the following observations it is concluded that they by their division give rise to lymphocytes:

1. The central groups of lymphocytes occupy similar positions to the plasmoidocyte groups (Fig. 1).

2. At the margins these groups of lymphocytes are directly continuous with the plasmoidocyte groups (Fig. 1.)

3. At this junction of lymphocytes and plasmoidocytes, dividing plasmoidocytes are especially to be seen, as if the change by division was occurring here.

4. There is a correlation between these two groups; when central "lymphocytes are abundant" plasmoidocyte groups are scanty and *vice versa*.

5. The lymphocytes of the central group have the characters of young cells. They have a scanty protoplasm, a small round darkly stained nucleus, and often show the kataphase condition of mitosis.

6. The return of lymphocytes to the circulation is associated with division of the plasmoidocytes in the gland, as is shown by the following experiment.

The prolonged exposure of an animal to radium irradiation or roentgen-rays results in a great destruction of lymphocytes through-

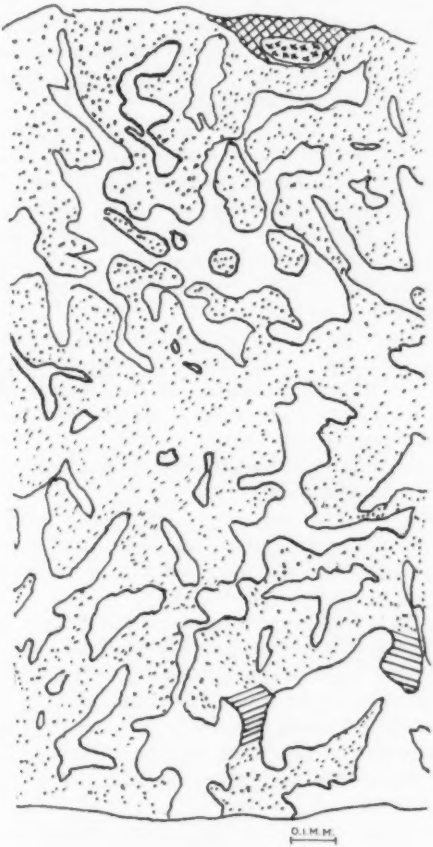

FIG. 5.—Projection of an iliac lymphatic gland after an exposure of the animal to 0.22 rads; the various cell groups are indicated as in Fig. 1.

out the body, so much so that sections of lymphoid tissues such as the spleen or lymphatic gland may fail to show a single lymphocyte (Fig. 5). It is evident that not only must existing lymphocytes have been destroyed, but also the production of fresh lymphocytes must have been inhibited. If lymphocytes are derived from the division of plasmoidocytes in the lymphatic gland of the rat, then

prolonged exposure to radium by inhibiting this division should result in the accumulation of these plasmoidocytes.

This expectation was found to be the case. After exposure to γ radiation for twelve days (0.22 rads), the inguinal lymph glands in the case of five animals were found to consist almost solely of plasmoidocytes, in some cases entirely.

It has already been mentioned that there is evidence that the cells of the follicles do not by division form lymphocytes, but have some other relation. The following facts suggest that they may become converted into plasmoidocytes:

1. It is possible to trace every intermediate stage between a macrophage cell of the follicle and a plasmoidocyte.

2. The macrophages gradually accumulate, by the digestion of lymphocytes, red granules in their protoplasm which have exactly similar staining qualities as the red granules of plasmoidocytes, and these granules tend from their first appearance to be deposited not near the nucleus, but toward the outside of the cell, as is the case with the plasmoidocytes.

3. It often occurs that the plasmoidocyte group extend right to the margin of the gland, and where this occurs neither marginal lymphocytes nor follicles are seen. In the absence of marginal lymphocytes, the follicle cells cease to divide, and their place is taken by plasmoidocytes.

4. The follicle cells are arranged around bloodvessels on exactly the same way as the plasmoidocytes are.

The functions, origin, and fate of the plasmoidocytes in the lymphatic gland have now been dealt with, and as regards the follicle cells, their function and fate have also been considered, only their origin remains to be discussed.

If a rat be given sufficient γ radiation to produce a profound lymphopenia, it has been seen that a few hours later a considerable accumulation of marginal lymphocytes occurs. If a further interval of time be allowed to elapse before the examination of the gland is made, then numerous young follicles will be seen. The following exposure was found to give good results: 100 mg. $RaBr_2 2H_2O$, screen 2 mm. lead, distance eight inches, time five days, animal killed at end of exposure.

Under these conditions, along the inner edge of the marginal lymphocytes will be seen numerous small bloodvessels and capillaries, lying among a network of lymphatic spaces, lined by endothelial cells. Detailed examination will show, that in many cases, lying in vacuoles of these endothelial cells are the nuclei of lymphocytes in the various stages of digestion shown in Fig. 6. It is here, in fact, that the early stages of this digestion are especially to be seen. Not only do these lymphatic endothelial cells (reticular cells) show this digestion, but also the endothelial cells lining the small bloodvessels.

As further evidence, that there is a close relation between a typical endothelial cell and the cells of the follicles, is the fact that every gradation from one to the other can easily be found, as shown in Fig. 7.

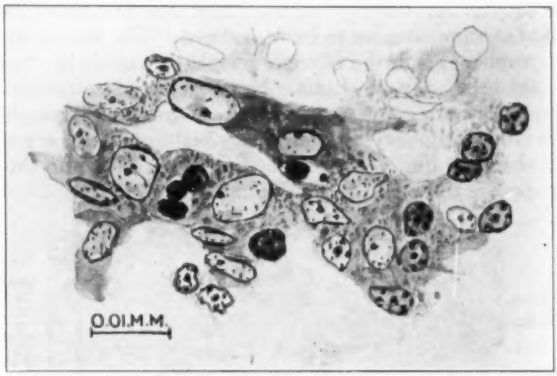

FIG. 6.—Endothelial cells lining a lymphatic channel, showing phagocytosis of lymphocytes.

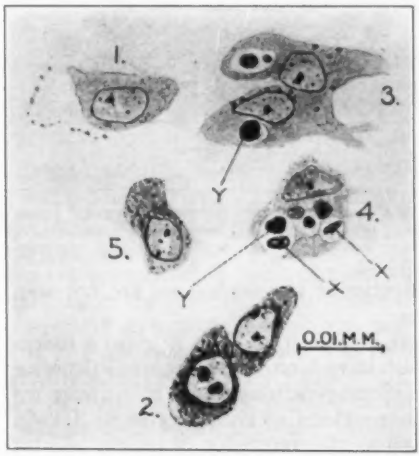

FIG. 7.—Shows transition from endothelial cell, 1, to follicle cell, 2, 3 and 4, endothelial cells phagocytosing lymphocytes; 5, endothelial cell intermediate in respect of granules between endothelial and follicle cell.

The follicle cell differs from the endothelial cell only qualitatively, the pale staining nucleus is common to both; both have one or two nucleoli, large in the follicle cells, small in the endothelial cell. In both the protoplasm is moderate in quantity and finely reticular,

it contains fine red granules when stained with eosinate of methylene blue, numerous in the follicle cell, and scanty in the endothelial cell. Other staining methods do not differentiate any qualitative difference.

The way in which the lymphocytes arising from division of the plasmoidocytes leave the lymphatic gland and find their way into the blood stream remains to be considered. The finding of many young lymphocytes in the efferent lymphatic vessels is strong evidence that this is a way of exit. Nevertheless examination of the bloodvessels running among the central groups of lymphocytes often reveals lymphocytes lying between the lining endothelial cells, as shown in Fig. 8. Thus this direct migration into the blood stream appears to be an alternative way.

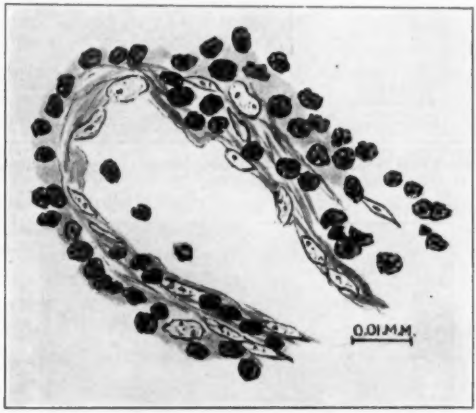

FIG. 8.—Portion of a small bloodvessel traversing a central group of lymphocytes, showing lymphocytes lying between the endothelial cells.

As before mentioned plasmoidocytes are not seen in either of these situations.

The accompanying diagram (Fig. 9) gives a concise view of the conclusions which have been drawn, the arrow denoting the direction of the changes. Some conclusions have been drawn with confidence, such as the phagocytosis of lymphocytes by follicle cells, others with doubt, such as the conversion of follicle cells into plasmoidocytes.

Lymphocytes, *L*, enter the gland by the afferent lymphatics, and are devoured by endothelial cells, *E*. These cells then gradually change into follicle cells, *M*; increasing in numbers by cell division, they next become converted into plasmoidocytes or myelocytes, *P*. The plasmoidocytes divide into lymphocytes, which leave the gland by the efferent lymphocytes, or possibly by the bloodvessels.

These observations have an important bearing upon the work being carried out at the Middlesex Hospital[2 3 4], and the Rockefeller Institute[5 6 7] upon the relation between lymphocytes and cancer immunity. For instance, at the Rockefeller Institute numerous communications have appeared showing that an exposure of animals to small doses of roentgen-rays and dry heat is followed by an increase in the number of mitotic figures in the corpuscles of the spleen and lymph glands, and this has been taken as evidence of a stimulation of lymphocytic formation, whereas according to the views here laid down, it is due to the accumulation of degenerated lymphocytes as a result of the treatment.

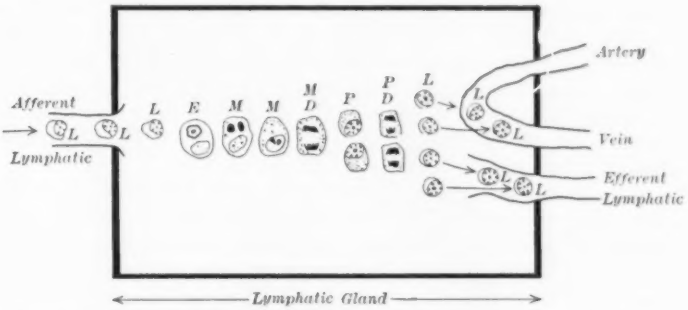

FIG. 9.—Diagram of the conclusions which have been arrived at. *L*, lymphocyte; *E*, endothelial cell; *M*, macrophage of follicle; *M D*, macrophage, dividing; *P*, plasmoidocyte; *P D*, plasmoidocyte dividing. The sequence of changes reads from left to right.

It may be mentioned that Murphy and his associates noted the degenerated and pyknotic lymphocytes surrounding the corpuscles. Further reference to their communication will reveal the fact that the lymphocytosis which follows exposure to roentgen-rays and dry heat does not correspond in point of time with the increased number of mitoses in the follicles. This occurs often many days before the lymphocytosis appears in the circulation, and they make special note of this discrepancy, namely the finding of increased mitosis, but without lymphocytosis.

It may be mentioned that two observers, Latta[8] and Maximow[9] have both recently concluded that the follicle cells phagocyte lymphocytes.

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THE PERMEABILITY OF THE INTESTINAL MUCOSA TO CERTAIN TYPES OF BACTERIA, DETERMINED BY CULTURES FROM THE THORACIC DUCT.

By Carl S. Williamson, M.D.,
DIVISION OF EXPERIMENTAL SURGERY AND PATHOLOGY,
AND
Rollo O. Brown, M.D.,
FELLOW IN SURGERY, MAYO FOUNDATION, ROCHESTER, MINN.

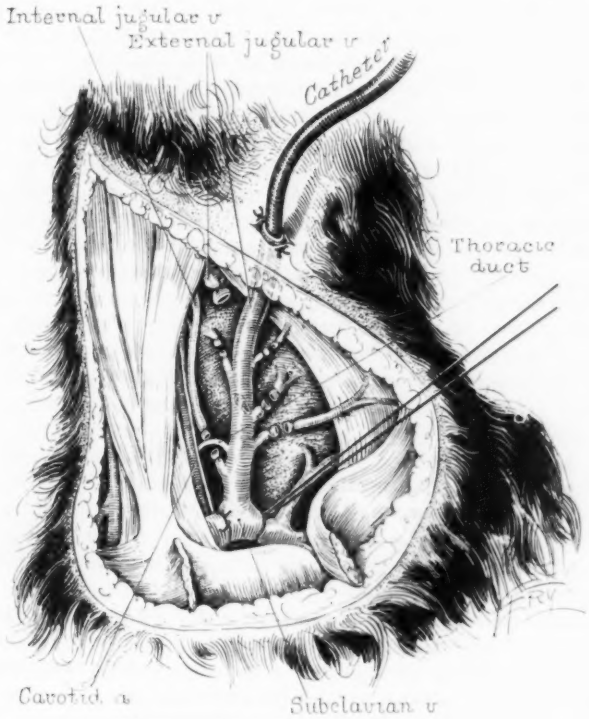
In many cases of pneumonia developing soon after operations in the abdominal cavity the cause is obscure. In view of the fact that bacteria producing chronic pulmonary lesions often gain access to the respiratory tract by way of the digestive tract and lymphatics, it occurred to us that the same route might be available to bacteria producing postoperative pneumonia. We, therefore, made the investigation which is described here.

An attempt was made to learn if bacteria introduced into the intestinal canal under normal conditions, and conditions comparable to operative procedures could be recovered from the lymph stream. The observations were made on dogs with thoracic duct fistulas. Sterile technic was used in all the operative procedures. The technic for making the thoracic duct fistula was modified from that employed by Biedl and will be described briefly.

Technic of Operation. The animal was fasted for from twelve to sixteen hours, and four to six hours before operation, it was fed a mixture consisting of 300 cc of milk and 200 cc of melted lard. In most instances the animal ate the meal readily, although it was necessary to give the mixture with a stomach tube to some. The meal of fat was given to stimulate the flow of lymph, to distend the lymphatic channels, and to make it easier to identify the thoracic duct. After sufficient time had elapsed, the animal was placed in an etherizing cabinet and anesthetized quickly in order to prevent vomiting; afterward it was placed on the operating table and ether was given by an anesthetometer. The maintenance of artificial respiration was necessary in case of accidental puncture of the pleura during the course of the operation. The purpose of this operation was to make the external jugular vein a conduit for the discharge of lymph, unmixed with blood, to the outside.

A straight incision was made over the left jugular vein extending from the middle of the clavicle upward to the level of the cricoid cartilage. The vein was then dissected free and all tributaries were ligated and sectioned. After the external jugular vein had been freed its junction with the internal was sought and the point of entrance of the thoracic duct located (see illustration). A ligature

was then placed around the venous trunk on the cardiac side of the entrance of the duct and another around the internal jugular vein about 1 cm. from its junction with the external. After all veins entering into the common jugular had been ligated, a ligature was placed around the external jugular near the upper border of the thyroid cartilage and the vein was sectioned below. The clotted blood was expressed from the vein and a flow of lymph was established. A soft rubber catheter was inserted into the vein, and



Diagrammatic sketch showing duct fistula.

the vein with its catheter was brought out through a stab wound in the skin and sutured in place with one or two silk sutures. In a few days the catheter came away, leaving a patent fistula.

It was possible, with careful handling, to maintain a flow of lymph for from two to four weeks, but in the majority of instances the fistula closed in about two weeks. Collateral circulation of lymph develops very rapidly in the presence of obstruction, hindering free discharge to the outside.

After the fistula was established, it was necessary to select an organism. It must be easily cultivated, not commonly found in the laboratory, nonpathogenic, and readily identified. Bacillus *prodigiosus* was chosen as the organism most nearly meeting all these requirements. The bacteria were grown either on dextrose-agar plates or in dextrose-bouillon. Cultures forty-eight hours old usually were used for injection. Bouillon cultures were employed in a few experiments only; they were fed or administered by stomach tube. The agar cultures were removed from the plates with as little agar as possible and placed in normal salt solution. This was well shaken to insure even distribution and administered by stomach tube. Attempt to estimate the number of bacteria for each unit of solution was not made. Control cultures were always taken before administration to insure the use of a viable organism. In the case of the salt suspension, the solution used contained enough organisms to make a definite pink color. The amount of suspension given varied from 20 to 30 cc for each dose. Before the bacteria were administered control cultures of lymph from the thoracic duct fistula were always made in order to rule out the possibility of contamination from the animal's cage. After feeding, cultures of lymph were made at hourly intervals during a period of from six to eight hours; in most cases cultures were made twenty-four and forty-eight hours after ingestion. All cultures were taken on sterile cotton swabs and plated on dextrose-agar plates. These were then incubated at room temperature for from twenty-four to forty-eight hours. Suspicious appearing colonies were subcultured and the organisms identified microscopically.

Experiments. Our experiments were divided into eight groups, each group comprising a minimum of five experiments and several groups containing from fifteen to twenty. The standard technic for culturing referred to was used in all experiments with the exception of the group in which the feces were cultures. The technic of this experiment is explained in the summary of Group 7.

Group 1. The animals were fasted for from twelve to twenty-four hours and then bacteria were administered with a small amount of food or, as in some instances, by stomach tube. The condition of the gastrointestinal tract in fasting animals is comparable to that obtained in man by preoperative fasting. All cultures in this group of experiments were negative.

Group 2. In many preoperative cases a purge of castor oil or magnesium sulphate is given. This causes some irritation of the intestinal tract, and might be a factor in allowing the passage of bacteria from the intestinal canal into the lymph stream. In this group of experiments 45 to 60 cc castor oil, or 15 to 20 gm. magnesium sulphate were given twelve to fifteen hours prior to feeding. The technic of feeding and culturing was the same as that employed in Group 1, and the same negative results were obtained.

Group 3. Certain observers have found that the permeability of the intestinal tract to bacteria is increased by certain types of food, particularly fat. By the technic used in the experiments in Groups 1 and 2, we attempted to determine the influence of diet on absorption of bacteria. Besides the bacteria, the animals were given diets rich in protein, fat, and carbohydrates, and some experiments were run in which the animals were on mixed diets. Cultures taken from animals on the various diets were negative for the ingested bacteria.

Group 4. Since we believed that the bacteria might be killed by the gastric juice during their passage through the stomach, it was desirable to obviate this possibility and at the same time, to introduce them near the beginning of the jejunum. This, besides lessening the concentration of the hydrochloric acid, would provide for maximal absorption. A loop of the jejunum, 15 to 30 cm. below the ligament of Treitz, was sutured beneath the skin ten to twelve days before the experiment was performed. A middle line incision was made under sterile technic, and the jejunum was brought up the desired distance from the ligament of Treitz. The recti muscles were sutured together beneath the loop of intestine with interrupted sutures of No. 2 catgut. Care must be taken to insure a sufficient opening at the point of exit from and entrance into the abdominal cavity. If caution is not used the points of exit and entry are apt to be too small and result in obstruction. It is also important, in drawing the edges of the recti muscles together, not to place the sutures too close together or to pull them too firmly else they are apt to obstruct the flow of blood to the transposed loop of intestine. We usually transpose a loop 12 to 15 cm. long and use four sutures to hold the recti together beneath it. After the edges of the recti were sutured together the subcutaneous fascia was closed with a continuous layer of catgut sutures. The skin was then closed with a continuous suture of linen. The wound healed in a few days and a thoracic duct fistula was made as in previous experiments. With a syringe and needle 20 to 30 cc of a salt solution suspension of bacteria were injected directly into the jejunum, which was readily felt beneath the skin. Cultures from these animals were entirely negative, showing that the gastric juice is not a factor in the negative cultures obtained from the lymph of the thoracic duct, and from the feces.

Group 5. In the experiments in Groups 1 to 5, the permeability of the normal intestinal tract to bacteria, exclusively, has been tested. In experiments of Group 5 we introduced a traumatic factor. Dogs with freely discharging duct fistulas were anesthetized and placed on the operating table, and the abdomen was opened. The viscera were brought out of the peritoneal cavity and exposed to the air for from fifteen to twenty minutes. In some instances, also, the viscera were rubbed with a dry gauze sponge until gentle

oozing occurred. At the end of the traumatic period, fifteen to twenty minutes, the bacteria, 20 to 30 cc of a pink solution, were injected by a hypodermic syringe directly into the stomach or, as in some instances, into the jejunum, and the abdomen was closed. The animal was then allowed to recover from the ether and cultures were taken as in the preceding experiments. Several cultures were positive, but in each instance the animal had vomited while recovering from the anesthetic and these positive cultures were regarded as contaminations. Cultures of the vomitus were positive. Trauma, then, did not make the intestinal tract more permeable to bacteria, as shown by cultures of the lymph from the thoracic duct.

Group 6. Realizing that the preceding experiments, while similar, are not comparable to operative procedures on the intestinal tract, we performed standard intestinal operations on dogs with fistulas as of the thoracic duct, for example, gastroenterostomies and end-to-end anastomoses. At the completion of operation bacteria were injected into the stomachs of the dogs with gastroenterostomies and into the intestines above the anastomosis in dogs with end-to-end anastomoses. Routine cultures taken following operation in this group of experiments were negative.

Group 7. Since absorption from the colon occurs, as demonstrated by rectal feeding and so forth, we decided to determine whether bacteria injected into the rectum could be recovered from the thoracic duct by culture. From 90 to 100 cc of the standard bacterial suspension was slowly injected into the rectum by means of a rubber tube, and in most instances the animals retained practically all of the injected fluid. However, routine cultures from the thoracic duct were uniformly negative for *Bacillus prodigiosus*.

We wished to learn if bacteria ingested as in the preceding experiments could be recovered from the feces, and, therefore, the feces of a few animals, two or three in each series, were cultured twelve, twenty-four, forty-eight, and seventy-two hours after ingestion. These cultures were always negative, showing that the ingested bacteria disappeared somewhere along the digestive tract.

Group 8. In this series of experiments eight animals with freely discharging ducts were used. From 20 to 30 cc of the standard bacterial suspension were injected with a needle and syringe directly into the peritoneal cavity, and routine cultures from the discharging duct were made. Positive cultures were obtained from four of the eight animals in from two to four hours after injection. This is the only group of experiments in the entire, comparatively large, series in which the results were positive.

Discussion. Much work has been done to show that bacteria pass from the intestinal tract into the blood stream, especially bacteria that produce chronic diseases. Ravenel, working with the bacillus of tuberculosis, recovered the organism from the blood after ingestion in a high percentage of instances. Diet was

a factor in the success of these experiments, that is, an animal fed on fat before or simultaneously with the bacteria always showed a greater number of positive blood cultures than did the fasting animal. Nicolas and Descas have also shown the influence of diet on the permeability of the intestine to bacteria as shown by culture of the blood.

In our experiments cultures of the lymph from the thoracic duct following ingestion of *Bacillus prodigiosus*, regardless of the diet of the animal, were always negative, as were cultures of the feces. Somewhere along the digestive tract the bacteria were destroyed or absorbed. We consider that, to a large extent, the germicidal action of the acid gastric juice was ruled out in the experiments of Group 4, but even these cultures were negative. However, it was not possible to rule out the destroying power of the digestive juices for the bacteria. The intestinal tract is host to many types of bacteria, but *Bacillus prodigiosus* is not among them, and it is entirely possible that a new organism in the intestinal tract is promptly destroyed by the action of the digestive fluids. On this point we can offer no direct evidence except to call attention to the countless varieties of bacteria that are constantly being taken into the body with the food, only a small number of which survive unless they are especially resistant, as is the bacillus of tuberculosis.

On the other hand, two other possibilities must be considered in accounting for the disappearance of the ingested organisms. These bacteria may pass through the intestinal villæ directly into the blood stream; but since our problem has to do only with the recovery of the ingested bacteria from a discharging thoracic duct, we have made no observations on this point. The other possibility is that the bacteria did pass through the intestinal wall with the chyle, but were destroyed, or came through in such small numbers by our method of culturing that they were not recovered.

Hess has shown that, if bacteria are injected into the colon and blood cultures made, it is necessary to use a large amount of blood in order to recover the bacteria. We believe that if bacteria come through the thoracic duct in such a small number as not to be detected by our method of culture, they could not be a factor in the production of postoperative pneumonia. Hess also determined that *Bacillus prodigiosus* injected into the rectums and colons of rabbits could be recovered from the upper digestive tract within a few hours after injection and also from the blood stream, if large amounts of blood were cultured. Ravenel and Hammer, in attempting to confirm the work of Hess, concluded, from a small series of experiments, that passage of bacteria from the rectum and colon into the blood stream is problematic. From observations on the possible passage of bacteria from the rectum and colon into the lymph stream we have reached the same conclusion as regards the lymph as Ravenel and Hammer reached in regard to the blood.

The experiments of Group 8 were made as control experiments on the passage of bacteria from the intestinal tract into the lymph. We, at present, are not prepared to discuss the significance of the passage of bacteria from the peritoneal cavity into the lymph; this will be dealt with in a future paper.

Conclusions. 1. It is not possible to recover *Bacillus prodigiosus* from a fistula of the thoracic duct by culture of the lymph after ingestion of the organisms.

2. The negative results were not influenced by diet or by trauma due to exposure of the viscera or to standard operative procedures.

3. Cultures of the feces for the ingested organisms were negative.

4. Cultures obtained from the thoracic duct following injection of the bacteria into the peritoneal cavity were positive in 50 per cent of the experiments of Group 8.

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A STUDY OF THE BILE OBTAINED BY NONSURGICAL BILIARY DRAINAGE, WITH ESPECIAL REFERENCE TO ITS BACTERIOLOGY.*

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It is our purpose in this paper to point out the information of practical clinical importance that may be obtained from a study of the bile collected by means of duodenal drainage. In 1919, B. B. Vincent Lyon[1] published a paper in which he showed how fresh bile may be obtained through duodenal drainage, basing this work of practical value upon a suggestion made by Meltzer[2] two years before in an article entitled "Disturbances of the Law of Contrary Innervation as a Pathogenetic Factor in the Diseases of the Bile Duct and Gall-bladder." Until recently, such a procedure would

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[1] Jour. Am. Med. Assn., 1919, **73**, 980.
[2] Am. Jour. Med. Sci., 1917, **153**, 469.

have been out of the question, for up to 1919 practically all studies upon the composition and bacteriology of the bile were made entirely upon bile obtained from the gall-bladder at operations or at autopsy, or through postoperative biliary fistulæ, with the exception of studies made on the fasting bile by Einhorn.

It will be recalled that in this connection Meltzer suggested the possibility of causing, through "crossed innervation," the paradoxical situation of relaxation of the sphincter of the common duct and at the same time contraction of the gall-bladder by the local application to the duodenum, by means of the duodenal tube, of a 25 per cent solution of magnesium sulphate. In making this suggestion, Meltzer but elaborated upon the well-proved physiologic observations made over twenty years before by Doyon and Oddi. To Lyon, however, belongs the credit of first making practical use of these physiologic and pharmacologic facts in diagnosis. He showed that when through a duodenal tube hyperisotonic solutions of magnesium sulphate are brought in contact with the duodenal mucous membrane and are withdrawn before absorption takes place, fresh bile may be obtained from the gall-bladder and bile ducts, and further that this bile may be separated into three definite fractions, *i. e.*, "A" bile which comes from the common duct, "B" bile which is of a different character and is derived from the gall-bladder, and "C" bile which is obtained from the hepatic ducts and bile capillaries and canaliculæ.

Abundant confirmation of his earlier work has been obtained by Lyon upon an enormous series of cases, and has been further confirmed by a large number of other observers. Thus there has been established a comparatively simple technic, by which with reasonable certainty fresh bile from various portions of the biliary tract may be collected through the duodenal tube. It is not too much to say that the method has become firmly established, and must be looked upon as a well-recognized and necessary additional method of gastrointestinal examination.

In passing it is perhaps fair to point out that the hypothesis advanced by Meltzer, and its further application by Lyon, have not been accorded uniform approval. There are those who question the validity of applying the law of "crossed innervation" to the gall-bladder and the muscle of Oddi. There are others who question whether the sphincteric action of the muscle of Oddi is definitely established and whether there is a specific action of magnesium sulphate in bringing about this relaxation and stimulation through intraduodenal excitation. Much stress is laid upon the fact that Meltzer's hypothesis is purely theoretical and has never been proved. The careful experimental work of Doyon and Oddi, in 1894 and 1895, seems to refute this latter contention. A thorough discussion of these moot points would here be out of place, but it is our belief, based upon personal observation and experience

with the method, in conjunction with increasing clinical and experimental evidence, that the principle enunciated by Meltzer and put to practical use by Lyon is in the main entirely reliable. An admirable critical discussion of the entire question has been furnished by Smithies, Karshner and Oleson.[3]

During the past year transduodenal lavage and stimulation of the flow of bile, by the introduction of hyperisotonic magnesium sulphate solution, has become almost a routine practice in the Gastrointestinal Clinic at the Graduate School of the University of Pennsylvania. In the course of this work we have met with the difficulties and disappointments from time to time that have been common to all workers in this field. On the whole our results have been encouraging and rarely has serious difficulty been experienced in introducing a duodenal tube into the duodenum. As a rule, not over an hour and a half has been required to get the tube in place. We have not had the difficulties claimed by some in determining the position of the duodenal tube. Without resorting to fluoroscopic examination we believe that the presence of the tube in the duodenum can usually be determined: (1) By the presence of the "duodenal tug," that is, when the tube is in the duodenum the plunger of the syringe attached to the free end of the tube will return to its position when traction is made upon it. Such is not the case, as a rule, when the tip is still in the stomach. (2) The appearance of pure yellow alkaline bile on aspiration or a lemon-yellow froth. (3) Failure to obtain water in the syringe after half a glass of water has been taken by mouth. (4) When the tube is in the duodenum, if 30 cc of warm water are allowed to run in and are then siphoned off by gravity the water will return definitely bile-stained. The latter method is particularly efficacious in those cases in which nothing can be obtained by aspiration due to a closed sphincter.

We have experienced but little difficulty in recognizing the three bile fractions referred to by Lyon, namely, the "A," "B" and "C" bile. Doubt has been entertained by some as to whether the dark bile alleged to come from the gall-bladder is actually derived from this source. In this connection observations, which are being carried out by one of us in conjunction with Dr. Eimann, of the Bacteriological Laboratories of the Presbyterian Hospital of Philadelphia, and which await later publication, are suggestive. Estimation of the cholesterin content of the various specimens of bile conclusively shows that in the dark gall-bladder bile the amount of cholesterin is approximately four and a half times greater than that obtained from either the common duct or hepatic duct specimens. This increased cholesterin content results from the concentration and stagnation of the bile which takes place in

[3] Jour. Am. Med. Assn., 1921, **77**, 2036.

the gall-bladder. The remarkable ability of the gall-bladder to concentrate the bile, and the restriction of this concentrating ability to the gall-bladder, has been admirably shown by the work of Rous and McMaster.[4] These authors have shown that bile is actually diluted in the bile ducts, whereas the gall-bladder is able to reduce the bulk of bile delivered to it as much as ten and two-fifths times in twenty-two and a half hours.

Five cases of cystic duct obstruction recently observed are interesting from this standpoint. The diagnosis in 3 of them was definitely confirmed, 1 by operation and 2 by roentgen-ray. There was no reasonable doubt about the diagnosis in the other 2. It was not possible to separate the bile into definite "A," "B" and "C" fractions, as there was no color change. In each case, however, the bile was collected in three separate bottles, the bottles being changed at the time when the color change usually occurs in normal cases. Each case was restimulated several times to be sure that no "B" bile was obtainable. In each case the amount of cholesterin in the three collected samples was practically identical. Compare these cholesterin readings with that for normal cases. In the latter the "B" fraction is always about four and one-half times as rich in cholesterin as the "A" and "C" bile. Its ratio is the same as that given by Hawk[5] in his table comparing the composition of liver bile and gall-bladder bile obtained directly from these organs. The "C" fraction usually contains about 10 mg. more cholesterin than the "A" bile, probably due to its being slightly mixed with the "B" bile. All of these cases had patent common ducts. An ample quantity of bile was drained from each. If this "B" fraction is due to liver stimulation or to magnesium sulphate, as has been claimed by some observers, why was it not possible to drain dark bile from these cases of cystic duct obstruction, there being no interference with the drainage of bile from the liver? If the "B" fraction is due to liver activity and not to concentration of bile in the gall-bladder, why was not the cholesterin content of the bile in the middle of the drainage four and one-half times greater than that obtained early and late in the drainage as it was in normal cases without cystic duct obstruction? Cases of this nature, which are constantly found in routine work, are decidedly convincing and seem to indicate that bile can be definitely separated into fractions, and that these fractions represent the bile from the common duct, gall-bladder and the hepatic duct system in that order. Whether or not the gall-bladder is emptied completely is not definitely known. We do not believe it is as a rule, for upon restimulating after having obtained the three fractions a small amount of gall-bladder bile will frequently be obtained the second time.

[4] Jour. Exper. Med., 1921, **34**, 7.
[5] Practical Physiological Chemistry, Seventh Edition.

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The technic employed by us for obtaining samples of bile for ordinary study is essentially the same as that advocated by Lyon and now widely employed. The method is so well known that detailed discussion seems unnecessary.

The accumulated observations of many workers during the last couple of years leave no doubt but that valuable data are obtainable from bile collected by the transduodenal route, from which, with a fair degree of accuracy, may be determined the state of the biliary tract. In order to be of value, it is generally conceded that the study of the bile must be carried out when the specimens are fresh. These studies may be grouped under three headings: (1) The gross appearance of the bile; (2) its microscopic appearance; and (3) its bacteriology.

When such examinations are carried out the following conclusions are justified as to the state of the biliary passages.

If the "A" bile obtained from the common duct is turbid and more viscid than normal and shows the presence of a considerable number of bile-stained epithelial cells of the tall columnar variety, less tall than gall-bladder epithelium, mucus, leukocytes and bacteria, it is suggestive of chronic common bile-duct infection.

The study of the "B" fraction is of the greatest significance. Grossly the normal "B" bile is clear, transparent, light amber to dark brown in color. It is free from shreds and gross detritus. The color change between the "A" and "B" fractions is usually sharp. The "B" bile is viscid and averages about 35 to 45 cc. Microscopically it may show an occasional cholesterin crystal or fatty acid crystal, particularly if allowed to stand. A slight amount of amorphous bile salt is frequently seen or an occasional epithelial element. It is not unusual to see elements, the identity of which cannot be determined. Any addition to this picture means, as a rule, some biliary tract pathology. Chronic cholecystitis, the most common condition encountered, causes alteration in the gross appearance of the "B" fraction. The bile is static, deep brown or black color, turbid and very viscid. It frequently contains gross detritus and flakes of mucus. For the microscopic examination one of these flakes should be selected. Microscopy will usually reveal the true condition of the viscus. The presence of clumps of degenerated bile-stained epithelial cells of the tall columnar variety associated with colonies of bacteria is diagnostic of cholecystitis. Frequently mucus, considerable unidentified detritus, leukocytes and pigment crystals add themselves to the picture. We have noticed frequently a considerable quantity of small rectangular prisms vary slightly bile-stained. Whether these are pigment crystals or bile salts we are not prepared to say. An abnormal amount of cholesterin crystals when *en masse* or in clumps is very suggestive of stones.

If the "C" bile shows the more marked departure from the

normal we should infer that the focus is either in the hepatic duct radicles or the liver. We have drained three cases of jaundice following arsphenamin injections and found the most marked change in the liver bile. After several drainings this was very noticeable, the freshly secreted bile coming last being very turbid and full of detritus and degenerated epithelial cells; no organisms were seen.

It must be borne in mind that frequently toward the end of the drainage a milky turbidity will develop, due to an ejection of gastric juice into the duodenum. Hydrochloric acid renders bile turbid. We have been unable to determine the cause.

If one is positive that the tube is in the duodenum and bile cannot be obtained following the stimulation, a hasty conclusion must not be drawn that common bile duct obstruction is present even when jaundice exists. Stimulate at least three times. Usually the sphincter of Oddi, for some reason, does not open until the second or third stimulation. We have noticed this particularly in two types of individuals, patients suffering from vagotonia and those with chronic cholecystitis. If after two or three drainages and the administration of belladonna bile cannot be obtained, a diagnosis of common duct obstruction may be made.

The repeated absence of the "B" fraction means cystic duct obstruction in the presence of a gall-bladder.

A careful study of the bile fractions as to their manner of appearing, the macroscopic and microscopic examination of the bile, all yield important information relative to the condition of the biliary tract.

From a diagnostic, prognostic and therapeutic standpoint, obviously great interest centers about the bacteriologic examination of the bile. A satisfactory technic for carrying out such an examination is obviously difficult, and many factors must be overcome before the result obtained can be regarded as reliable. In numerous instances we have attempted bacteriologic studies of the bile. In an effort to have these observations as reliable as possible the following technic, after the method advocated by Lyon, has been adopted.

The night before the examination is to be made the patient must brush the teeth thoroughly; the mouth and throat are carefully washed by lavoris (weak astringent solution of ZnCl and formalin), followed by liquor antisepticus. From then on no further food or fluid is ingested and the tube is passed the following morning on a fasting stomach. Prior to the passage of the tube the throat and mouth are thoroughly disinfected by lavoris followed by liquor antisepticus. The duodenal tube, having been rendered sterile by careful surgical sterilization, is then passed by an operator wearing sterile gloves and a sterile gown. As soon as the duodenal tube has reached the stomach the stomach is

carefully washed with distilled water until the return is entirely clear. It is next washed with a solution of lavoris, 60 cc being diluted with 200 cc of sterile water. This lavage is followed by another lavage of sterile water. Then 250 cc of a 1 to 1000 silvol solution are introduced into the stomach and removed. This is followed by another lavage with sterile water, which is continued until the return flow is entirely clear. Such fluid or contents as is then remaining in the stomach is cultured and the duodenal tube allowed to pass into the duodenum. Before stimulation with magnesium sulphate a culture is made from the duodenal contents. Then stimulation of the duodenum is carried out as usual, with 75 cc of a 25 per cent solution of sterile magnesium sulphate. The bile is then obtained in the usual way, being segregated in the three fractions "A," "B" and "C," from all of which separate cultures are made.

By following this method it is generally possible to render the upper alimentary tract sterile for all practical purposes. By taking cultures from the stomach and duodenum, and possibly the mouth and throat, before stimulation is made, one is enabled to know which, if any, organisms are present in these structures before the flow of bile begins. Exceptionally the only organisms obtained from the bile are the same as those obtained from the stomach or duodenum before the bile has entered it. Under such conditions the organisms found cannot be regarded as in any way peculiar to the bile, and the cultures should be repeated. If the cultures obtained from the bile contain only the commoner mouth saprophytes such as the Streptococcus salivarius, Micrococcus catarrhalis or the Bacillus subtilis, no significance can be attached to the findings, which must be looked upon as due to contamination. The organisms, which, however, are of importance and which have been repeatedly isolated by numerous observers, include streptococci, especially the hemolyticus, the Staphylococcus aureus and albus, the Bacillus typhosus and the colon bacillus. From the somewhat meagre published results of bacteriologic examination of the bile thus obtained it is surprising to note the frequency with which some observers have found hemolytic streptococci. It is also interesting to note that pneumococci have been reported by some, which seems somewhat incomprehensible in view of the well-known bile-soluble property of pneumococci.

It must be admitted that the technical difficulties, as well as the rather meagre knowledge at present available as to the bacteriology of the stomach, duodenum and biliary passages, often make the bacteriologic study of the bile distinctly unsatisfactory.

Elaborate and careful experimental studies on the bacteria, and the static and germicidal properties of the bile have been carried out by Neilson and Meyer.[6] Their experiments were largely done with

[6] Jour. Infect. Dis., 1921, **28**, 542.

test-tubes and included a variety of biles from different animals, such as cats, goats, rats, dogs, oxen, sheep, pigs, and a few observations on bile obtained from man. The human specimens were obtained wholly from cholecystectomized bladders or by aspiration during a laparotomy. These observations were made largely upon organisms of the typhoid-dysentery-paratyphoid group and the vibrio of cholera. In the specimens of bile obtained from man they found that the typhoid bacilli grew well and remained viable for more than ten days, whereas with the cholera bacillus it required eight days before the sterilization was complete. They concluded that the vigor of bacterial growth in average human cystic bile is noteworthy. They further discovered that proliferation is somewhat influenced by artificially reducing hydrogen-ion concentration, but that complete suspension of growth only occurs at a pH_4, which in all probability never occurs in a human body. The importance of their paper, so far as man is concerned, has largely to do with the influence of cystic bile on the human typhoid carrier state.

It was originally our intention to discuss the bacteriologic findings in a series of cases that exhibited disease of the biliary tract or gall-bladder, but in the earlier portion of our work so much difficulty was experienced with the bacteriologic technic that the results obtained were regarded as too unreliable for permanent record. We have, however, had an opportunity of carrying out some successful and interesting bacteriologic observations on a limited number of cases, and in order to demonstrate the importance of the bacteriologic findings in the bile these cases will be reported briefly.

Case I.—C. P., Jr., aged sixty years. On January 1, this man suffered from a gastrointestinal disturbance associated with marked jaundice. A diagnosis was made by his physician of acute catarrhal jaundice. In the course of two weeks the jaundice entirely cleared up. The patient first came under observation by us three weeks after the onset of his jaundice. At that time there was no evidence of jaundice on physical examination. Stools contained bile and the urine was free of it. He exhibited, however, considerable pallor. There was some elevation of blood-pressure; he suffered from a distinct asthenia, coated tongue and loss of appetite. Examination of the urine showed the presence of considerable quantities of albumin, numerous hyaline and granular casts and red blood cells. He was admitted to the hospital apparently suffering from an acute exacerbation of a chronic nephritis. Hematuria became more marked and the anemia progressed, Careful search was made for a focus of infection that might be held responsible for the acute renal manifestations. All possible foci of infection were eliminated except the gall-bladder, over which there

was a slight persistent tenderness. With the history of a recent attack of jaundice it was decided that the gall-bladder was in all probability the focus of infection responsible for his progressive anemia and his renal symptoms. Three weeks after coming under observation his hemoglobin was 55 per cent; his red cells 2,860,000 and his leukocytes 17,100. At this juncture duodenal drainage was instituted. A considerable quantity of dark gall-bladder bile was obtained. In this bile were found numerous flakes of mucus, much sediment and epithelial cells. In 3 of the specimens of gall-bladder bile pus was present. On culture on two separate occasions Staphylococcus aureus and albus were found in pure culture in the "A," "B" and "C" bile, and these organisms were not present in the cultures taken from the stomach or from the duodenum before stimulation was resorted to. It was also interesting to note that specimens of urine collected under sterile conditions at about the same time and examined at a different laboratory also gave pure cultures of the same organisms. There seemed, therefore, to be some justification for the assumption that the gall-bladder and renal infections were the result of the same organism. Owing to a steadily falling blood count the patient was given a transfusion of 500 cc of blood. Some slight improvement followed this procedure, although the blood count did not noticeably increase. The most marked subjective improvement followed biliary drainage, which was practised once a week. A vaccine was prepared from the strains of Staphylococcus aureus and albus isolated from the bile. During the past month the patient has been receiving the vaccine every four days. The hematuria has cleared up, the renal symptoms have subsided, the blood count has shown marked improvement and subjectively the patient presents every indication of recovery.

Case II.—E. D., aged fifty-two years, in whom a diagnosis of duodenal ulcer and cholecystitis was made. The condition of the gall-bladder was discovered by a biliary drainage during a course of two weeks' treatment with duodenal feeding. In this patient the microscopic study of the bile showed a considerable number of pus cells, bile-stained epithelial cells, many short motile bacilli, a few pigment crystals and quantities of amorphous bile salts. Bile from the gall-bladder was obtained by the aseptic technic of Lyon. Cultures showed a luxurious growth of colon bacilli. An autogenous vaccine of colon bacilli was prepared and injections were given at intervals of four days up to 1,000,000,000 bacilli. At the same time weekly biliary drainage was practised. The original culture was obtained on January 13. On March 23, a second culture, obtained by the same technic, was sterile. At this time the patient was symptomatically greatly improved. Gastrointestinal symptoms had disappeared.

CASE III.—A woman, aged thirty-five years, was suffering from chronic arthritis of eleven years' duration. After exhaustive search for the foci of infection, in the course of which the tonsils were removed and some teeth extracted without improvement, nonsurgical drainage of the biliary tract was instituted. The "B" bile was a deep brown black, very viscid, contained many shreds and particles and on culture showed Streptococcus hemolyticus and Staphylococcus albus in luxurious growths. In view of these findings the gall-bladder, regarded as the probable focus of infection, was removed. At operation no stones were found but a definite chronic cholecystitis existed. Cultures taken from the gall-bladder at operation showed hemolytic streptococcus and Staphylococcus albus. Confirmation by surgical means of the findings obtained by the transduodenal drainage are interesting and significant of the value of the latter method. Biweekly biliary drainage was instituted in this case. Two months after the original culture was obtained from the bile, bile cultures were again made following the Lyon antiseptic technic. This time the Staphylococcus albus alone was present; the streptococcus had disappeared. An autogenous vaccine was prepared and given. A month later the biliary drainage was discontinued and the patient at that time was showing marked improvement; her temperature was practically normal and she was able to be up and to walk about. It is interesting to note in this case that after the cholecystectomy no "B" bile was obtained and absolutely no color change in the bile. We have never observed dark bile sooner than six months after cholecystectomy.

CASE IV.—K., aged sixty years. This patient was suffering from a chronic arthritis. Her tonsils had been removed without results. Biliary drainage was instituted and cultures were obtained according to the Lyon technic. A nonhemolytic streptococcus was isolated from the "B" bile. Stomach cultures were sterile. A vaccine was made and is being administered. The patient is still under observation, and although improving it is too early to know the ultimate result.

CASE V.—M., aged fifty-three years. The patient gave a history of recurring attacks of slight jaundice and so-called "biliousness." These latter attacks he had since his youth. Biliary drainage was instituted and cultures made from the bile. In this instance, although the bile showed Staphylococcus albus, nonhemolytic streptococci and unidentified micrococci were also found in the stomach cultures. The results obtained from the biliary culture were too uncertain to justify any therapeutic procedure based upon these findings without further checking the results. This case is cited to emphasize the importance of culturing the stomach, even though it is believed to be sterile. Even though a different organ-

ism had been isolated from the bile it could not be regarded as significant, since the stomach was not sterile.

These cases have been reviewed in order to point out the possibility of accurate bacteriologic study of the bile by means of biliary drainage and also to again emphasize the frequently forgotten role that the gall-bladder plays in producing focal infection.

The checking by operative findings of the results of biliary drainage in Case II is a gratifying evidence of the reliability of bacteriologic studies made by this technic. A much more impressive example, however, of the value of preoperative duodenal findings in comparison with the lesion found at operation is furnished by Whipple,[7] who, in a series of 27 cases on whom careful studies of the biliary tract were made by means of duodenal drainage before operation, found a striking coincidence in the operative findings with those obtained by a study of the bile before operation.

In carrying out our bacteriologic studies of the bile a caution which has been rightly emphasized by Lyon should be pointed out. Lyon insists upon the importance of replanting from the original broth culture, if one is used, in six hours. If this is not done a rapidly growing colon bacillus may render it extremely difficult to isolate the slower growing streptococcus, should such an organism be present. In order to render the bacteriologic examination doubly safe, bile is planted on broth cultures during the biliary drainage and is transplanted within twelve hours. In addition to this all the bile withdrawn is collected in bottles, separated into "A," "B" and "C" fractions, and streak cultures are made from these fractions on solid media at once. By following this method the isolation of these organisms will be facilitated.

Conclusions. 1. We believe that the method of biliary drainage instituted by Lyon and based upon the hypothesis of Meltzer is a useful and practical procedure, and that there is every reason for the belief that the bile obtained in this way is derived from the common bile duct, the gall-bladder, the hepatic duct and the biliary capillaries in the order given.

2. In our experience the diseased condition of the gall-bladder and the bile ducts can be recognized in this way by a microscopic and bacteriologic study of the bile, which under pathologic conditions shows alterations which are significant.

3. The bacteriologic study of the bile derived in this way is feasible and is of importance, but in order to be successful a rather elaborate, time-consuming technic is essential.

4. If such a technic is carried out the bacteriologic findings are useful and serve as a guide to therapeutic procedure.

Finally, however, it should be emphasized that it is our feeling

[7] Ann. Surg., 1921, **73**, 556.

that the information obtained by nonsurgical biliary drainage is only a diagnostic adjunct, and in no sense should take the place of a careful history and complete physical examination. It is only when the findings derived from biliary drainage are taken in conjunction with a complete clinical study of the case that accurate conclusions can be drawn. Our knowledge of the bacteriology of the biliary and upper gastrointestinal tract is still so meagre that a great deal of work and much careful observation will be required before this phase of the subject is placed upon an entirely satisfactory basis.

EXPERIENCES WITH NONSURGICAL BILIARY DRAINAGE.

(MELTZER-LYON TEST.)

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IN 1917, Meltzer published a theoretical discussion of his views regarding the interrelation between the gall-bladder musculature and the sphincter of Oddi. He invoked the general physiological "law of contrary innervation" (which applies to other neuromuscular reflexes of the alimentary tract), to explain their interplay as antagonists in the normal storage and discharge of gall-bladder bile. He drew an analogy between the action of the gall-bladder and that of the urinary bladder, in that, when the bladder contracts the sphincter relaxes, and when the sphincter contracts the bladder relaxes. To substantiate his contention, he cited the experiments of Doyon,[2] showing the crossed innervation of the gall-bladder and Oddi's sphincter within the splanchnic and vagus nerves.* In a small footnote appended to his paper (which bears repetition because of its frequent misquotation), Meltzer[1] stated:

"In experiments with $MgSO_4$, I observed that the local application of a 25 per cent solution of that salt on the mucosa causes a completely local relaxation of the intestinal wall. . . The duodenal tube, however, apparently has reached an efficient, practical stage. I make, therefore, the suggestion, to test in

* Because of the technic employed, Doyon could not demonstrate a contraction of the gall-bladder and a relaxation of the sphincter in the same experiment. He believed that normally they must be practically simultaneous. A consideration of the pressures involved, substantiates this view. Freese[30] found the maximum force of gall-bladder contraction to be 313 mm. of water, whereas Archibald[31] found the resistance of the sphincter to vary between 500 to 650 mm. of water and McWhorter[32] found its maximal value to be 580 mm. of water.

jaundice and biliary colic the local application of a 25 per cent solution of $MgSO_4$ by means of the duodenal tube. It may relax the sphincter of the common duct and permit the ejection of bile, and, perhaps, even permit the removal of a calculus of moderate size, wedged in the duct in front of the papilla of Vater."

It should be noted that Meltzer made no mention of observations on gall-bladder contraction in response to magnesium sulphate. Frequent statements and misquotations that he did, have constantly appeared in the literature.

The Work of Lyon. B. B. Vincent Lyon, correlating the above pregnant suggestion with the "law of contrary innervation," studied the effects of douching the duodenal mucosa with magnesium sulphate solutions injected through a duodenal tube. In a practical communication,[3] he concluded that Meltzer was correct in his application of this law and that it was possible, in normal people, to obtain a fractional separation of the bile from the various portions of the biliary tract. Thus, he stated, it was possible to segregate the gall-bladder, or "B" bile, from the common duct, or "A" bile, and the hepatic duct, or "C" bile. By careful examination (physical, chemical, microscopical and bacteriological), a definite diagnosis could be made of pathological conditions in these portions of the biliary system. In a series of articles,[4, 5, 6, 7, 8, 9] Lyon elaborated a method of diagnosis and treatment of the gall-bladder and ducts heretofore undreamed of.

Criticisms. The subject was immediately taken up by various workers and dissenting opinions were soon expressed. Thus, Einhorn[10, 11] studied the return following the injection of various salts through the duodenal tube, and plotted the values of the color intensity, alkalinity and specific gravity of the bile. He concluded that increases in these values represented liver stimulation through portal absorption and liver excretion of the injected salts. He also claimed that aqueous solutions of 25 per cent magnesium sulphate, 25 per cent sodium sulphate, 25 per cent glucose and 5 per cent peptone possessed the property of marked liver stimulation, whereas 25 per cent sodium phosphate, 13 per cent magnesium citrate, 15 per cent magnesium sulphate, 0.5 per cent sodium chloride, and many other substances, stimulated the liver to lesser degrees. He disagreed with Lyon that these values represented gall-bladder admixtures. It is proper to state that Einhorn's theory is contrary to the evidence of experimental studies of the excretion of magnesium salts,[12] and that he formulated it from clinical data only.

Bassler,[13] failing to observe definite contractions of the exposed gall-bladder after laparotomy under ether anesthesia, came to practically the same conclusions. Both authors also observed a return of dark bile following magnesium sulphate in some cholecystectomized patients, and used this fact as a further argument

against the gall-bladder origin of the "B" bile in the non-operated case.

Crohn,[14] failing to obtain gall-bladder contraction in narcotized dogs, doubted the gall-bladder origin of the "B" bile.

Dunn and Connell,[15] in a case of hepatoduodenostomy, injected magnesium sulphate solution through a duodenal fistula into the duodenum and also into the jejunum, and obtained a dark bile fraction with an increased magnesium content. They concluded that portal absorption and hepatic excretion of the salt were the most plausible explanation of their findings.

Discussion of Criticisms. These "criticisms" when correlated with the known facts of experimental physiology are incorrect deductions from observations, rather than true objections to the fundamental principles of the reaction. To explain the source of dark bile which is occasionally obtained in cholecystectomized patients, Doyon[2] demonstrated that the bile ducts, as well as the gall-bladder, can contract. Rost[16] showed, in cholecystectomized dogs, that those developing continence of Oddi's sphincter (with concomitant dilation of the ducts), reacted to injections of peptone in a manner somewhat similar to dogs with intact gall-bladders. He proved, by comparison with the failure of response in dogs with incontinent sphincters, that the bile ducts were stimulated reflexly to discharge their pent up bile. He further showed that after several months, these continent dogs exhibited organic dilatation of the bile ducts, even to the formation of new gall-bladders. These findings have been corroborated by other observers.[17, 18] Since stasis of bile with moderate increase in its color concentration can occur in the ducts, their contraction will result in the discharge of bile of darker color than bile direct from the liver.

The case of Dunn and Connell appears convincing only on superficial examination. It may be interpreted as a reflex discharge of static bile from the hepatic ducts. It must be remembered that this was a case of severe biliary infection of several months' duration, in which damage to the biliary ducts had undoubtedly occurred. As to the increased values of the magnesium content of their so-called "B" bile, which they assume was absorbed and excreted by the liver, sufficient evidence was not adduced, first, that there was no reflux into the duodenum of the magnesium sulphate injected, and second, that the gram-molecular increase of Mg over that of SO_4, in the proportion of $MgSO_4$, was not due to the increased magnesium content of the static duct bile itself. This could have been done by the comparison of the findings following peptone injection.

That magnesium sulphate solution introduced into the duodenum does not proceed directly onward as is usually assumed, can be demonstrated by coloring the injected fluid. In 10 cases, I introduced 75 cc of 33 per cent magnesium sulphate, colored with

2 cc of 2 per cent methylene blue, and syphoned out the fluid immediately. Throughout the discharge of "B" and "C" biles, lasting from one-half to three-quarter hours, irregular jets of bluish to greenish watery bile were obtained, and the bile between these jets showed less or no coloration by the dye. It is also the admixture of such small amounts of the original magnesium sulphate solution throughout the reaction, that can account for the markedly increased specific gravity of the "B" bile, as compared with the actual specific gravity of the gall-bladder content at operation. Thus, as small an amount as a 5 per cent solution of magnesium sulphate in bile will increase its specific gravity from 1013 to 1055.[10]

Regarding the failure to observe actual gall-bladder contraction during operation under anesthesia, it should not be forgotten that we are dealing here with a delicate neuromuscular reflex, which, analogous to the pupillary and conjunctival reflexes, can be abolished according to the depth of the anesthesia. Bainbridge and Dale[19] appreciated this fact and refrained from drawing conclusions from their failure to elicit reflex gall-bladder contractions in their anesthetized animals. Doyon, however, succeeded in registering such reflex contractions following irritation with vinegar and ammonia in curarized (non-anesthetized) dogs. This fact has been overlooked recently by several experimenters.

Gall-bladder Response to Duodenal Irritation. Doyon found that irritation of the gastric and duodenal mucosa caused a relaxation of the common duct sphincter and a contraction of the gall-bladder. This fact can explain the varying colored bile responses following the injection of various chemicals into the duodenum. In studying this phase of the subject, I selected cases in which the "B" return was distinctly atypical, affording a sharp contrast to the "A" and "C" biles, *viz.*, "B" biles of a very dark or tarry appearance, or with special microscopical characteristics. Nine such patients were operated on. Successive injections (from 2 to 4) of various solutions during the same intubation were given, 60 cc being injected and immediately syphoned off. It was found that besides 25 to 33 per cent magnesium sulphate (which acted most energetically, probably because of its peculiar property of relaxation), 5 to 10 per cent peptone, 25 per cent glucose (and occasionally and much more feebly, 25 per cent sodium sulphate), produced similar "B" biles, which were similar to the gall-bladder contents at operation. These are the substances that Einhorn claims possess the property of marked stimulation of the liver. After injection of 15 per cent magnesium sulphate, 13 per cent magnesium citrate, 25 per cent sodium phosphate, and 0.5 per cent sodium chloride, biles which were slightly darker than the fasting liver bile control were usually obtained; but *the same result* was also occasionally observed *after plain water* injected at a temperature slightly above that of the body. Also following successive injections (2 to 3)

of these weaker solutions during the same intubation, a distinct "B" return was sometimes obtained, similar to that following 25 to 33 per cent magnesium sulphate or 5 to 10 per cent peptone. In tests made *in vitro* all of these colors could be simulated by mixing various amounts of gall-bladder contents with "C" bile. Furthermore, 7 of the cases which showed a distinctly atypical "B" bile, were studied six to sixteen weeks after cholecystectomy, and *then not one showed a "B" bile.* The inference is forced upon us, that in accordance with the findings of Doyon, these darker specimens are due to varying amounts of gall-bladder bile, dependent upon the strength of gall-bladder contraction coincident with sphincteric relaxation in response to the injected irritant.*

Although Meltzer failed to observe intestinal relaxation if magnesium sulphate solution passed through the stomach, yet with the duodenal tube *in situ*, after swallowing 75 cc of 33 per cent magnesium sulphate, the sequential flow of "A," "B," and "C" bile is usually obtained, though it is not as forceful as when the magnesium sulphate is injected through the tube. Its action is similar to that following the injection of a less hypertonic solution.

To test Lyon's suggestion of the hormonic action of magnesium sulphate, 10 patients were given intramuscular injections in the amount advised in the treatment of tetanus.[10] Intravenous injections were considered too hazardous. Fifteen cc of 25 per cent magnesium sulphate (and in 1 case, 15 cc of 50 per cent solution, due to nurse's error) were injected deep into the gluteal region. No gall-bladder response was observed in any case from one-half to three-quarters hours (at which time in the rabbit full systemic effects occur[21]). Some patients complained of feeling heavy and tired. Otherwise, no effects were noted.

Lyon described "B" bile as bile from the gall-bladder admixed with bile from the liver. That "B" bile is not a uniform fluid, as it should be if it were excreted by the liver, is readily demonstrated in cases with gall-bladder stasis by viewing it in a test tube against a ground-glass background immediately after its return. Whirls of dark colored and viscid bile in a lighter and more limpid bile can be distinguished. In a few minutes, however, the mixture becomes uniform and is of a lighter color than the gall-bladder bile found at operation. In normal cases there is not sufficient color contrast between the gall-bladder bile and the liver bile to bring out such a reaction so distinctly.

Because of this admixture, comparison of the "alkalinity" of the "B" bile with that of the gall-bladder bile, always gives a higher value for the latter. A static gall-bladder bile has an increased nucleoprotein content, which combines with HCl, result-

* Spasm of the sphincter may be brought about by *strong* irritation, mechanical or chemical. According to McWhorter,[31] hyperacidity will produce a spasm of the sphincter. Similar observations are recorded by Archibald.[32]

ing in very high titrations for the "alkalinity." As high as 200 cc $\frac{N}{10}$ HCl (calculated for 100 cc of bile, methyl orange indicator), was obtained in 1 case.

Disadvantages of Magnesium Sulphate in Diagnosis. In studying the effects of different substances injected into the duodenum, it was found, that while magnesium sulphate proved to be the most energetic in causing a gall-bladder response, it has serious diagnostic disadvantages. If after the completion of the reaction to 5 per cent peptone, 25 to 33 per cent magnesium sulphate be injected and a comparison of both samples of "B" and "C" biles be made, it will be found that those specimens obtained after the use of the hypertonic magnesium sulphate are usually contaminated with numerous duodenal flocculi. This occurs even if the duodenum was previously douched with astringent solutions (0.2 per cent zinc chloride or Lavoris). Microscopical examinations (stained and unstained) of these flocculi show very numerous short columnar and cuboidal cells, varying numbers of polymorphonuclears, and rare red blood cells, frequently together with many organisms enmeshed in strands of mucus. It is most likely an osmotic reaction of the mucous membrane to the hypertonic salt, for similar response can be obtained by any strongly hypertonic salt. It is interesting to note that the tall columnar cells, which line the villi, are very few in number, and that the cytological picture is that of exfoliated cells from the deeper portions of the crypts of Lieberkühn. This is not surprising if we bear in mind the fact that inflammatory reaction is most marked in regions where drainage is poor and bacterial nests can form. As the epithelial lining of the biliary tract is histologically similar to that of the duodenal mucosa, and as disease of the gall-bladder is usually associated with an exfoliative duodenitis, to avoid confusion it *is essential to recognize the cellular contamination from this region.* Furthermore, since these duodenal flocculi contaminate the aspirated bile specimens, the bacteriological studies of them must be very misleading regarding the true status of biliary infection. While cultural studies were not made, the microscopical comparison of the specimens of "B" and "C" biles after 5 per cent peptone, with those obtained after the strongly hypertonic salt (consecutive injections during the same intubation), substantiates this criticism. A *priori*, I would suggest, that cultural studies on specimens after 5 per cent peptone injection will give more exact data regarding biliary infection.

Technic. In the early cases, the original plan of Lyon was followed, but after becoming familiar with the details of the test, and with the appearance of extra-hepatic contaminations, the preliminary washings and sterilizations of the stomach were omitted, simplifying the method to meet the demands of outpatient practice. The patient presents himself with a twelve-hour fasting stomach. The relation of the test to previous feeding is important and has

not been sufficiently emphasized, for, as Rous and McMaster[12] have shown, the concentration of gall-bladder bile is continuous and dependent on the duration of its sojourn in that organ. After obtaining a specimen of fasting gastric juice, the tube is swallowed slowly, as suggested by Lyon, until the bulb is in the duodenum, which usually takes from one-half to two hours. To determine whether entrance into the duodenum has been effected, roentgenological examination is the best method, but for obvious reasons, it is not practicable for routine work. The litmus test is not entirely reliable, for regurgitation of duodenal contents into the stomach may cause a bluish tinge, and again, the tube may have entered the duodenum and yet an acid reaction is not infrequent. Of the various tests suggested, I have found the most reliable to be the failure to recover swallowed water, or to recover less than half of 90 cc injected through the tube. But in cases of gastroptosis in which the fluid may gravitate beyond the bucket, this too might be misleading. However, when once familiar with the appearance and reaction of the bile, together with the manner of return of swallowed or injected fluid, one can, in most cases, form an accurate judgment regarding the position of the tube.

The duodenal fluid is permitted to syphon into a series of 20 cc test tubes, a separate tube being used for every change in the character of the fluid. As many as 25 tubes may be required during a test, thus obtaining a veritable cinema of the bile discharge. A specimen of the fasting duodenal contents is examined for comparison with later specimens. It has been my experience that bile can be obtained from the fasting duodenum in most cases, even in normal persons. Schneider[23] reports similar findings. Lyon, however, interprets bile in the fasting duodenum as indicating "a lesion of group organs physiologically related to this intestinal zone." Bruno[24] stated that, in animal experiments, no bile appears in the fasting duodenum. However, it is probable that with the tube, the irritation of the metallic bulb causes sufficient relaxation of even a normal sphincter to permit bile to flow from the ducts. Ordinarily, the stimulus is too weak to cause gall-bladder contraction. However, in a small percentage of cases, spontaneous discharge of small amounts of deeper colored gall-bladder mixtures may occur. (Einhorn,[25] attempted to diagnose the condition of the gall-bladder from such specimens.) It is important to recognize that in the same individual, bile samples from the fasting duodenum are of varying color (from light straw to golden yellow), depending on varying dilutions, chiefly by duodenal fluid and gastric juice. One should not designate as "B" bile, the darker samples of "C" bile.

After securing a sample of the fasting duodenal contents, the duodenum is lavaged with 90 cc water at body temperature for the purpose of washing away any superficial mucus, etc. For reasons

already given, the gall-bladder response is stimulated by the injection of 60 cc of 5 per cent peptone.* Because of its bland action on the duodenal mucosa, peptone affords a more exact analysis of the various components of the bile tract. We can, with more certainty than after magnesium sulphate, venture an opinion regarding the origin of muco-flakes appearing in the "A," "B," and "C" biles. Thus, the attempt to locate the source of disease is made more practicable. Occasionally, the gall-bladder response to peptone is slow, sometimes not appearing until a half hour after the injection. Occasionally, 10 per cent peptone is effective when 5 per cent fails. Following the reaction to peptone, I always inject 75 cc of 33 per cent magnesium sulphate in order to determine the degree of duodenitis present, and to restimulate gall-bladder discharge. A second or even third injection of 25 cc of 33 per cent magnesium sulphate is given if no gall-bladder response occurred after the previous injections. It is remarkable to what degree exfoliative duodenitis is usually associated with gall-bladder disease. The duodenal flocculi frequently sediment to one-quarter the volume of bile in some of the test tubes. This reaction to the strongly hypertonic salt usually manifests itself quickly, but sometimes, it may not develop fully until after twenty to thirty minutes. Occasionally, no gall-bladder discharge occurs after either 5 or 10 per cent peptone, but following the relaxing effect of magnesium sulphate on the intestinal wall, a forceful flow is obtained. Following the reaction to magnesium sulphate, no further injection or lavage is given, and no ill effects have been noted from the absorption of toxic material. This is not surprising, since most of the bile is syphoned out of the tube.

The entire reaction must be closely watched, as the tube may be dislodged by a cough, sneeze, etc., and thus vitiate the findings; or small amounts of gastric juice may appear, which must be segregated. Furthermore, the examinations must be made immediately, since oxidation takes place quickly with clouding of the bile. Since only a few minutes are required for serious alterations or even complete destruction of the important cellular elements by the pancreatic ferments, there should be as little delay as possible in the microscopical examinations.

Diagnosis. The practicability of making a diagnosis depends upon one's familiarity with the reaction in normals, and revolves about the careful examinations and *comparisons* of the fasting gastric, and duodenal fluids, and the "A," "B," and "C" biles. The examinations include the following: (1) *Physical*, quantity, color, transparency or turbidity, viscosity, manner of discharge,

* An unrefined peptone is not effective. While Witte peptone is the best preparation, it is too expensive for routine use. I have found that a good preparation by any reliable firm, such as Armour or Eimer and Amend, is equally effective as Witte peptone in stimulating gall-bladder response.

flocculi, presence of sand; (2) *microscopical* (oil immersion on stained and unstained specimens essential for the study of the cellular and bacterial content), epithelium, leukocytes, red blood cells, mucus, bacteria, inflammatory débris, and crystals; (3) *chemical*, alkalinity (methyl orange indicator).

In normal subjects (if the sphincter is closed), 10 to 20 cc of clear light golden-yellow bile, "A" bile, is followed, after one to three minutes, by 1 to 3 ounces of syrupy darker transparent amber bile, "B" bile, and then a varying quantity of light clear golden-yellow bile, "C" bile. Microscopically, there are present occasional epithelial cells, leukocytes, bacteria, scattered bile crystals and traces of mucus from the duodenum or bile. Changes from the *normal* findings indicate *malfunction or disease*.

The diagnosis may be made by the correlation of the following observations:

1. Failure to obtain bile after successive stimulations indicates occlusion of the common duct.

2. The volume of "A" bile is dependent on the time interval between the injection and the gall-bladder response, as well as on the degree of dilatation of the common duct.

3. Failure to obtain "B" bile in *repeated* tests is indicative of an organic condition which is interfering with the function of the gall-bladder. This finding, in conjunction with the clinical picture, is a distinct indication for surgical intervention.

4. Sand or agminated crystals, is evidence of a tendency toward or of the actual presence of stones.

5. Swarming or colonizing bacteria indicate active infection.

6. Increased number of or massed leukocytes is indicative of an acute or subacute inflammatory reaction. The use of 2 per cent acetic acid brings out the nuclei more clearly.

7. Darker colors of "B" bile, clear to slightly turbid, (deeper shades of amber to tarry black), with sluggish or intermittent discharge, yielding more than 90 cc or less than 20 cc, are indicative of various degrees of gall-bladder stasis. Lyon interprets this finding as evidence of gall-bladder atony. However, occasionally cases are encountered in which no gall-bladder discharge occurs after peptone, but following the relaxing effect of magnesium sulphate on the intestinal wall, a *forceful* flow occurs. Such a reaction suggests that the primary condition present is not one of atony of the gall-bladder musculature, but rather one of increased tone or spasm at the ampulla with consequent (contrary) relaxation of the gall-bladder as originally suggested by Meltzer. It is frequently associated with varying degrees of duodenitis. Such a condition might well be termed "ampullospasm," analogous to spasms at other sphincters, *viz.*, pylorospasm, cardiospasm, etc. The gall-bladder stasis in relation to this spasm is analogous to the gastric retention in relation to pylorospasm.

It must be pointed out that in cases with sluggish gall-bladder discharge, the resulting "B" specimen will consist chiefly of liver bile and only a small proportion of gall-bladder bile. It is evident that the resulting mixture will be much lighter than the gall-bladder content.

In many cases of gall-bladder stasis, repeated gall-bladder responses to successive injections of peptone were obtained (as many as 6 injections and responses in 1 case). In these, a definite interrelation between the gall-bladder and pylorus was evident. During each discharge of "B" bile, the pylorus remained closed, and cloudy precipitation of the bile by acid gastric juice appeared only after "C" bile was obtained. In relation to this observation, it is interesting to note the frequency after cholecystectomy of regurgitation of bile into the stomach. This gastric bile (if retching was not present), is an indication of disturbed physiology about the pylorus.

8. Columnar cells, especially tall columnar cells, usually degenerating, deeply bile stained, and in fan or rosette formation, when present *only* in the "*B*" *fraction*, represent catarrhal desquamation from the gall-bladder. Frequently intensively bile-stained detritus is also present.

To designate a particular group of cells as derived specifically from the gall-bladder is a difficult task, especially since all recent evidence, clinical and pathological, tends toward the view that chronic cholecystitis is usually associated with inflammatory reactions in the liver and pancreas. However, with increasing experience and care in the technic as described above (careful segregation and comparison of specimens), it can be done.

It should be pointed out that the depth of bile stain bears no constant relation to the origin of a cell from the gall-bladder. Examination of gall-bladder contents frequently shows varying degrees of bile staining of the cells, whereas in reflux bile into an acid stomach, cells become deeply stained. This can be reproduced by adding 2 per cent acetic acid or strongly acid gastric juice to colorless duodenal cells in bile.

9. Mild gall-bladder colic soon (and in some cases a few hours later), after the injections, indicates an inflammatory condition of the gall-bladder.

10. Regarding cultural studies, Whipple's[26] results show that contaminations from the mouth and stomach are unavoidable in many cases, even with the most careful technic. There were conflicting findings in about 50 per cent of his cases. From his results, I conclude, that when gross infection (direct microscopical evidence) is absent, cultural methods are not reliable.

It is necessary to emphasize that a light-colored bile may show marked microscopical evidence of disease, whereas a dark bile may show nothing more than its increased color concentration. The

gall-bladder, in disease, may even lose its property of concentrating bile.

It is also necessary to emphasize that this method of investigation enables us to make a diagnosis of early gall-bladder disease when the clinical signs and symptoms are slight and vague. At exploration the surgeon fails to detect this type, for he cannot judge the normality of the organ by sight or touch. I have observed 3 cases in which the surgeon pronounced the gall-bladder normal, but changed his opinion on further examination of the aspirated bile or after the removal of innocent looking adhesions. Judd,[27] in 1916, was suspicious of this fact, and recently Einhorn and Meyer,[28] reported a series of 18 cases of recurrent cholecystitis without stones, from which they concluded that it is not the appearance or softness of the gall-bladder, but rather the examination of the aspirated bile, that is the true criterion of its condition.

Clinical Experience. During the past two years, 415 successful intubations were performed in 128 patients, chiefly gall-bladder suspects. Most of these tests were performed in the outpatient service devoted to the study of gastrointestinal diseases conducted by Dr. Edward A. Aronson, to whom I am indebted for many courtesies.

Normal reactions were obtained in 45 cases, of which 20 were normal persons selected for the study of normal findings; in the remaining 25 cases, roentgen-ray examination proved the presence of calculi in 2, and in 5 others the history and clinical studies were highly suggestive of a chronic cholecystitis. The finding of a normal reaction in chronic cholecystitis has also been reported by Brown.[29] It is a question for future experience to decide, whether with our better understanding of the pathogenesis of gall-bladder disease (removal of foci of infection and relief of biliary stasis), these cases with normally functioning gall-bladders may not carry their evidences of past dysfunction safely without surgical intervention.

The other 83 cases were classified as follows:

I. Repeated absence of "B" bile—22 cases.

This finding is interpreted as evidence of advanced organic disease as discussed above.

II. Abnormal microscopical findings ("B" bile)—19 cases.

On this evidence these cases were classed as cholecystitis or cholelithiasis. In cholelithiasis the examination frequently shows only the findings of the associated cholecystitis. The direct indication of the presence of or tendency toward calculi (sand or agminated crystals) is frequently lacking. In these cases the correlation of the bile examination with a carefully taken history, roentgen-ray examination and other clinical findings is essential to the diagnosis of stones.

III. Static "B" bile (without abnormal microscopical findings) —37 cases.

On the basis of the test, these cases could be classed only as functional (?) atony of the gall-bladder or "ampullospasm." Many cases of enteroptosis were included in this group. Many cases presented the clinical picture of the functional type of relative atony described by Lyon: Vague dyspepsias, so-called "biliousness," often associated with attacks of migraine. Also included in this group, were 7 cases in which the clinical diagnosis of chronic cholecystitis was considered certain. In 2 cases, gall-stones were definitely present and in 1 case stones were found at operation. The differentiation between these clinical types could be made only by the correlation of the test with other clinical data (history, roentgen-ray findings, etc.). The finding of static "B" bile without definitely abnormal microscopical elements, while indicating gall-bladder dysfunction, cannot be interpreted as evidence of definite gall-bladder disease. The elucidation of this large group requires further study, especially of the chemistry of the bile (cholesterin, nucleoprotein content, etc.).

Operation was performed on 17 patients. This group in which our findings were corroborated is most instructive. Operation was advised in 11 patients solely on the evidence of the fractional bile examinations. In these 11 patients either the gall-bladder condition was merely suspected, or an incorrect clinical diagnosis had been made. In 8 of the patients, "B" bile was not obtainable after several attempts, and the operative findings disclosed sufficient gall-bladder disease to account for the failure of the gall-bladder response. In the remaining 9 patients, the *"B" bile* and the *gall-bladder contents at operation* corresponded both in color and microscopical findings. In 7 cases of this group, I had the opportunity to repeat the test six to sixteen weeks after the cholecystectomy, and *then "B" bile could no longer be obtained.*

Besides these, 5 other cholecystectomy cases were studied, and in only 1 (operated on two and a half years previously) was a "B"-type of bile discharged. In this case I obtained 45 cc of light brown bile. However, its manner of discharge was different from that of static bile from the gall-bladder, in that it did not present the whirls of dark bile within a lighter bile as described before. Although stasis of bile in the hepatic ducts is not frequent, it must be borne in mind that it can occur. To differentiate it from gall-bladder bile, its manner of discharge must be closely observed, and here, as in other cases, the findings must be correlated with the history (previous operations), physical examination (presence of icterus), and other clinical data. If such precautions are not taken, errors in interpretation will be made.

Discussion of Cases. (See Table I). Cases I, III, IV, V, VIII, and XIV were clear-cut clinical cases of cholelithiasis. In Case V the only explanation for the failure to obtain "B" bile was the presence of very viscid tarry bile in a thickened gall-bladder. In

TABLE I.

Patient.	Clinical diagnosis.	Meltzer-Lyon test.	Findings at operation.	Repetition of test 6 to 16 weeks later.
1. Mrs. M. S.	Gall-stones	No "B" bile; G. B. colic; exfoliative duodenitis	G. B. full of stones	
2. Mrs. B. R.	Chr. cholecystitis?	No "B" bile; G. B. colic; increased leukocytes after injection	Cystic duct stone; G. B. content mucopurulent	
3. Mrs. S. P.	Gall-stones	No "B" bile; exfoliative duodenitis	Cystic duct stone; G. B. many stones	
4. Mr. H. W.	Gall-stones	No "B" bile	G. B. full of stones	
5. Mrs. F. F.	Gall-stones	No "B" bile	Thickened G. B.; viscid tarry bile; 3 stones	
6. Mrs. R. H.	Suspicious G. B. 1 yr. later obstructive jaundice	No "B" bile; no bile in duodenum	Infiltrating Ca. involving G. B., stomach and pancreas	
7. Mr. H. M.	Duodenal ulcer	No "B" bile; severe G. B. colic	Stone in cystic duct; G. B. content mucopurulent	
8. Mrs. Y. K.	Gall-stones	No "B" bile; exfoliative duodenitis	G. B. full of stones; G. B. content mucopurulent	
9. Mrs. D. R.	Gall-stones	2 tests: No "B" bile 2 tests: Greenish-black "B" bile with agminated cholesterin crystals. Flocculi of degenerating tall columnar cells. Exfoliative duodenitis	G. B. appeared normal. Few small stones in cystic duct and many small stones in G. B. contents similar to "B"	No "B" bile.
10. Mrs. B. F.	Chr. cholecystitis?	Greenish-black "B" bile. Flocculi of deeply-stained columnar cells and scattered cocci and leukocytes enmeshed in mucus. Agminated cholesterin crystals. Marked exfoliative duodenitis	Many small stones in G. B.; contents similar to "B"	No "B" bile.
11. Mrs. C. K.	Postop. adhesions; recurrent chr. cholecystitis?	3 tests: No "B" bile 2 tests: Black bile with swarming bacteria, clumps of leukocytes and intensively stained detritus; G. B. colic	Acute cholecystitis; adhesions between G. B. and anterior abdominal wall; contents similar to "B"	No "B" bile.
12. Mrs. R. G.	Appendectomy 12 wks. before, G. B disease not suspected	Tarry black bile; macroscopical sand; marked exfoliative duodenitis	Many small stones in G. B. contents similar to "B"	No "B" bile.
13. Mrs. E. L.	Duodenal ulcer; G. B. (?)	Deep amber clear bile; many agminated cholesterin crystals; small flocculi of columnar cells and deeply-stained detritus; G. B. colic; exfoliative duodenitis	Normal G. B. to sight and touch; small adhesion at fundus; later more small adhesions found; strained bile, 8 small stones; G. B. contents deep amber, clear. Microscopical examination not made	No "B" bile.
14. Mrs. M. B.	Gall-stones	Clear, static (deep brown) "B" bile; no microscopical findings. Marked exfoliative duodenitis	Many small stones in G. B.; contents similar to "B"	Not done.
15. Mrs. C. S.	Hyperthyroidism; gastroptosis	Turbid amber bile; many scattered degenerating columnar cells; many bacilli; scattered leukocytes; agminated cholesterin crystals; detritus	Thickened G. B.; no stones; contents similar to "B"	No "B" bile.
16. Mr. J. R.	1, Luetic crises? 2, Gastric ulcer? 3, G. B.?	Greenish-black bile; small flocculi of degenerating deeply stained columnar cells; exfoliative duodenitis	Three stones in G. B.; contents similar to "B"	No "B" bile.
17. Mrs. A. H.	Appendectomy 4 mos. before	Static (greenish-black) viscid "B" bile; no microscopical findings; marked exfoliative duodenitis	No evidence of disease by sight or touch; aspirated bile similar to "B"	Not done.

Case XIV, clinically cholelithiasis, only the evidence of marked stasis was found in the examination of the "B" bile. In Case II, in several tests, a definite increase in clumped leukocytes was found in the bile following the injection of peptone. These cells were interpreted as evidence of inflammatory reaction in the ducts.

In Cases II, IX, and X the diagnosis of probable chronic cholecystitis had been made clinically. The marked anomalous bile fractions that were obtained made the diagnosis of gall-bladder disease certain. In Case IX, at operation, the gall-bladder appeared and at first felt perfectly normal. However, on careful palpation a few small stones were felt low down in the cystic duct. After extirpation, the gall-bladder was found to contain numerous small stones practically suspended in the bile. It is interesting to note that in two tests no "B" bile was obtained in this case.

Case VI, a very obese woman, complained only of belching after meals, and disease of the gall-bladder could only be suspected. As "B" bile was absent in several tests, the diagnosis of definite organic disease of the gall-bladder was made and operation was urged. Because of her slight symptoms, this was refused. One year later she developed persistent jaundice with complete absence of bile in the duodenum. On exploration, a huge infiltrating carcinoma involving the gall-bladder and invading the stomach and pancreas was found. This case is instructive in that the definite diagnosis of organic disease of the gall-bladder, demanding operation was made one year before the clinical evidence manifested itself. It is a question whether the operation, when first advised (solely on the basis of the repeated absence of "B" bile), might not have saved this woman.

Case VII presented the three cardinal symptoms of duodenal ulcer: Pain two hours after meals, night pains and an "interval history" of several years duration. This diagnosis had been made by three well known gastroenterologists, and the patient had been subjected to a regimen of duodenal alimentation for cure of his ulcer without relief. On duodenal stimulation of the gall-bladder, no "B" bile could be obtained. The injection was followed by severe colic in the gall-bladder region requiring injections of morphine for its control. The patient was then referred for operation with a definite diagnosis of gall-bladder disease, and a subacute empyema with a calculus occluding the cystic duct was found.

In Case XI, a cholecystostomy had been performed four years before coming under observation. Interpretation of the patient's symptoms was difficult because of her markedly neurotic condition, and also because they might have been simply and readily explained by postoperative adhesions. Duodenal examination revealed a "B" bile with swarming bacteria, an increased number of leukocytes, and inflammatory débris. Gall-bladder colic followed the test.

Reoperation was advised. While under observation prior to the operation acute cholecystitis developed, the temperature rose to 104° and immediate operation became imperative. At operation acute cholecystitis was found with adhesions between the gall-bladder and the anterior abdominal wall. These adhesions could account for the failure to obtain "B" bile in three of the tests.

In Case XII, an appendectomy had been performed twelve weeks previously without relief of symptoms. Gall-bladder disease had not even been suspected, as the complaints were referred to the right lower quadrant of the abdomen.

Case XIII, clinically, was considered most probably one of duodenal ulcer. From the "B" bile examination, the diagnosis of cholecystitis with the probable presence of stones was made. At operation, the gall-bladder appeared and felt perfectly normal, but after dividing an innocent looking adhesion at the fundus many more small adhesions became evident. After removing the gall-bladder and straining the bile, 8 small stones were found.

Case XV was one of hyperthyroidism and gastroptosis. With this diagnosis her abdominal symptoms had been explained for many years. The "B" bile showed definite microscopical evidence of disease. At operation chronic cholecystitis was found.

Case XVI was a man with a luetic history and a positive Wassermann reaction. The differential diagnosis lay between luetic crises, gastric ulcer, and possibly, gall-bladder disease. The tubal findings indicated the last. At operation only cholelithiasis was found.

Case XVII, a woman, aged thirty-four years, complained of midepigastric "burning" for two years. Appendectomy was performed four months previously without relief of symptoms. The tubal findings showed a clear, but very static greenish-black viscid "B" fraction without special microscopical features. This was associated with a very marked exfoliative duodenitis. Because of the markedly static bile and the persistence of symptoms, it was believed that gall-bladder disease was present. Because of the patient's objection to medical treatment, reoperation was advised. At operation the gall-bladder showed no external evidence of disease, but the aspirated bile proved to be of a static, greenish-black color similar to the "B" specimen. A cholecystostomy was done, and after surgical drainage for three weeks, the symptoms were completely relieved. It is now three months since the operation. The pathology of the gall-bladder of this case is, of course, undetermined. As far as our data go, the case was one of marked gall-bladder stasis and exfoliative duodenitis. It is probable that as much could have been accomplished with medical drainage.

Summary and Conclusions. 1. Criticisms of the fundamental principles of the Meltzer-Lyon test can be answered, and do not bear strict analysis.

2. Because of its bland action on the duodenal mucosa, 5 per cent peptone is suggested for diagnosis in preference to strongly hypertonic magnesium sulphate solutions.

3. Attention is drawn to the condition of "ampullospasm" in relation to gall-bladder stasis.

4. A normal reaction may be present in chronic cholecystitis. However, in most cases of gall-bladder disease we observe either failure of gall-bladder response, or microscopical abnormalities, or evidence of stasis. The correlation of these findings with other clinical data is essential to a correct diagnosis.

5. The practicability of the test is presented in 17 operated cases. In many cases, the definite diagnosis of gall-bladder disease cannot be made by any other method.

6. Since gall-bladder disease, with its protean clinical manifestations, is a frequent cause of intra-abdominal symptoms (second only to disease of the appendix), this test should be included as a routine in the study of gastro-intestinal cases.

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STUDIES OF GRAVES' SYNDROME AND THE INVOLUNTARY NERVOUS SYSTEM.

II. The Clinical Manifestations of Disturbances of the Involuntary Nervous System (Autonomic Imbalance).

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Introduction. Comprehensive understanding of the involuntary nervous system requires a study of the phylogeny, embryology and physiology of vertebrates. These arduous and important tasks have been performed mainly by Gaskell's[1 2 3] and Barger and Dale.[4] Gaskell has compiled the literature in his monograph on the "Involuntary Nervous System," and the following review is a condensation and rearrangement of his data. The rearrangement was necessitated by the fact that Gaskell wrote not with a view to the

clinical study of the involuntary nervous system, but to establish the origin of the vertebrate ancestor.

PHYLOGENY AND EMBRYOLOGY OF THE INVOLUNTARY NERVOUS SYSTEM. The cells of the involuntary nervous system arise from those of the cerebrospinal axis. Phylogenetically the involuntary nervous system makes its first appearance in the annelid and it is noteworthy that this is the first phylum in which a vascular system is developed. Of the cells of the primitive involuntary nervous system one group retains as its function the transmission of nerve impulses; the other develops into the chromaffin tissue and acquires secretory activity. In the higher vertebrates the chromaffin cells collect in the adrenal medulla while the nervous cells retain for the most part their segmental arrangement.

ANATOMICAL AND PHYSIOLOGICAL DIFFERENCES BETWEEN THE INVOLUNTARY AND VOLUNTARY NERVOUS SYSTEM. In the voluntary nervous system the motor cell is in the anterior horn and the nerve that emerges in the anterior root is a medullated effector fiber.

In the involuntary nervous system the motor cell occupies a position outside the cord and the medullated fiber that connects it with the central nervous system is a connector and not an effector fiber. The migrated cell gives origin to the true effector fiber, which is non-medullated and is called postganglionic. Whereas the impulse in the voluntary nervous system passes from the cerebrospinal axis to the end-organ without interruption, in the involuntary nervous system it is relayed at the peripheral ganglion. Physiologically the systems differ in that the involuntary nervous system usually functions without entering consciousness and is uninfluenced by the will. "The more the concentrated voluntary nervous system (brain) is freed from the insubordinate involuntary nervous system consistently with the harmonious interaction between the systems, the greater the advantage to the animal." (Gaskell, page 23.)

THORACICO-LUMBAR AND BULBO-SACRAL SUBDIVISIONS OF THE INVOLUNTARY NERVOUS SYSTEM. The involuntary outflow takes place from the midbrain, medulla and thoracico-lumbar and sacral cords. The thoracico-lumbar forms one subdivision and is separated from the others by the plexuses for the limbs. The other three outflows are grouped as the bulbo-sacral division.

It is Gaskell's theory that the ancestor of the vertebrate presented a double segmentation, appendiceal and branchial. The branchial segmentation has given rise to the structures of primitive endoderm and the appendiceal to the structures of primitive ectoderm and mesoderm. The appendiceal segmentation has given rise (1) to the appendages of the skin and the subdermal layer of musculature, (2) the vascular system, including the heart, and (3) the derivatives of the segmental duct from which arise the organs of excretion and reproduction. These structures function for individual and race preservation. They receive excitatory impulses via the thoracico-

lumbar and are stimulated by adrenalin. The bulbo-sacral innervation is antagonistic. The branchial segmentation has to do with the metabolic functions in the organism inasmuch as its important derivatives are (1) the gastro-intestinal tract and its accessory glands, and (2) the respiratory tract and such appendages as the thyroid, parathyroid and thymus. Most of these structures receive augmentor impulses over the bulbo-sacral and are accordingly stimulated by acetylcholin. The thoracico-lumbar sends inhibitory impulses to many of these same structures and adrenalin suppresses their functional activity.

Factors that Maintain the Tonicity of the Involuntary Nervous System. With the discovery of the specific action of adrenalin on the thoracico-lumbar division of the involuntary nervous system, nothing was simpler than to assume that its tonic activity was regulated by the epinephrin circulating in the blood. The quantitative work of Hoskins[5] demonstrated quite clearly that adrenalin in amounts sufficient to cause a rise of blood-pressure, inhibits intestinal movement. Hence, the tonicity theory was generally abandoned and for it was substituted the emergency theory of Cannon.[6] This postulates that in times of stress epinephrin is poured forth to stimulate the thoracico-lumbar division. The experimental work of Cannon and his colleagues, however, has not been confirmed by other workers, notably Stewart and Rogoff.[7] For the present Cannon's[8] ingenious theory may be regarded as interesting and stimulating, but not proved.

It has been assumed that some metabolite, possibly a cholin derivative, in an analogous manner regulates the tonicity of the bulbo-sacral division.

Our own[9] work fails to show the factors concerned with the maintainance of the tonus of the thoracico-lumbar; the tonus is quite independent of the adrenals, and we think that the amount of epinephrin necessary to produce an emergency effect is beyond the secretory capacity of the adrenal glands.[10] We have also been unable to confirm the reported stimulating effect of thyroxin[11, 12] on the involuntary nervous system, and we have shown that in acute experiments, at least, thyroxin is quite without effect on the involuntary nervous system.

Autonomic Imbalance. The following report deals with patients whose symptoms can be ascribed to disturbance in the realm of the involuntary nervous system. The symptoms may be divided into three groups. In the first of these the symptoms are objective, and due to disturbed function of an organ in which no lesion can be demonstrated by the most painstaking clinical examination. The second group differs only in that the manifestations are subjective. The third group is composed of such symptoms as asthenia and tremor. Their constant association with the above groups and their accentuation by adrenalin administration has led us to regard them as of similar origin.

To the syndrome presented by the association of these symptoms we have applied the term *autonomic imbalance*. In it we include the conditions ordinarily called larval hyperthyroidism, forme fruste of hyperthyroidism, Basedowoid, suprarenal insufficiency, etc. These terms are discarded because they are either misleading, or are dependent on an erroneous or doubtful hypothesis.

Material Studied. The 86 patients reported, (Table I) were studied in the Outpatient Department of Mount Sinai Hospital.* None had definite or constant elevation of their basal metabolism but all had autonomic imbalance as we have defined it.

Etiology. 1. *Predisposing Causes.* The factors that predispose to this syndrome are at present unknown. Manifestations of the disturbance have been present in most of these patients as far back as they can remember. Whether the predisposition is inherited or whether it is due to some early environmental factor remains to be decided.

2. *Exciting Causes.* As exciting causes may be mentioned: (*a*) sex epochs; (*b*) focal infection; (*c*) psychic insult.

(*a*) In 23 of the 86 patients the symptoms were greatly accentuated at the time of puberty. In 11, pregnancy aggravated the symptoms. Hence in 40 per cent of these patients exacerbation was associated with a sex epoch.

(*b*) In 2 patients infection was the most probable etiological factor. In nearly one-half of the patients focal infection was present and may have been an exciting factor. Forty-one of the patients had tonsils from which we expressed secretion, and 7 had sinus infections.

(*c*) Psychic insult played an essential role in 8 patients and a minor role in at least 12 others.

Symptoms. A. Subjective Symptoms. 1. *Palpitation.* Thirty-nine patients complained of palpitation. There was no relationship between this symptom and the pulse rate: for example, No. 8613, a woman whose pulse was 70 and whose basal metabolism was—2, had palpitation and No. 8579 with a pulse rate of 140 had no palpitation.

2. *Dyspnea.* Eleven women complained of shortness of breath. Of these 7 had auricular extrasystoles, but in none of the others could any disturbance of the cardiac or pulmonary mechanisms be elicited, and in none was there any elevation of the basal metabolism.

3. *Headache.* Seven women had chronic or recurring headaches; in 1 sinus infection evidently played a role; in the others no cause for the headache could be found.

4. *Insomnia.* The insomnia was sufficiently marked in 20 patients to demand treatment.

5. *Loss of Weight.* Thirteen patients reported loss of weight.

* We wish to express our appreciation to Miss May Slater, R.N., who, as Superintendent of the Outpatient Department, rendered invaluable assistance in the organization and maintenance of our clinic.

B. Objective Symptoms. 1. *Diarrhea.* Four women, all over thirty years of age, reported attacks of "diarrhea." No dietetic or physiological cause for the intestinal disturbance was present.

2. *Eye Signs.* Von Graefe's sign was present in 19 women and in 12 others there was a definite exophthalmos.

3. *Gastric Disturbances.* Eight women complained of "indigestion." In many of these there was a close simulation of the symptoms of gastroduodenal ulcer or of chronic appendicitis. The relationship of the alterations in the involuntary nervous system to these unclassified gastric disorders will be the subject of a later communication.

4. *Menstrual Disturbances.* Menstrual disturbances of various types were reported by 5 patients.

5. *Sweating.* Abnormal degrees of sweating were present in 17 patients. In 2 instances the profuse night sweats led to the erroneous diagnosis of tuberculosis.

6. *Vasomotor Instability.* Blushing, flushing, or cold extremities pointed to vasomotor instability in 10 patients.

7. *Mental Disturbances.* Emotional instability was common. Psychoneurosis was present in 12; it usually assumed the anxiety or sexual types.

8. *Tachycardia.* Only 2 patients of this group had a pulse rate below 80. In the majority, the most striking objective findings were the tachycardia and the extreme lability of the pulse rate. Thus in patient No. 3598 the range was from 96 to 200. The tachycardia was most marked in the group of the puberty patients, where a rate of from 140 to 160 was not at all uncommon. It is noteworthy that the tachycardia bears no relation to palpitation or to the basal metabolism. Thus patient No. 8539 had a pulse rate of 104, palpitation, and a basal metabolism of −6; No. 8633 had a pulse rate of 120, palpitation, and a basal metabolism of 0; No. 8680 had a pulse rate of 136, palpitation, and a basal metabolism of +10; No. 8547 had a pulse rate of 130, basal metabolism of +8, and no palpitation.

9. *Irregularities of Cardiac Mechanism.* Cardiac irregularities were present in 6 patients. Auricular extrasystoles were the most common (3 patients). One patient (No. 8740) had a paroxysmal tachycardia and another (No. 9235) paroxysmal auricular flutter. All of these patients were referred by Dr. Rothschild from the Cardiac Clinic where they had previously been examined. The absence of any organic cardiac basis for their symptoms was verified clinically, by fluoroscopy and electrocardiogram, before the patients were sent to us. Most of these women had been regarded as "cardiacs" for years. Small doses of atropine gave (Nos. 8498, 8740, 9235) prompt relief. A further study of this group will be made by Dr. Kaufman Wallach and their relationship to the "cardiac war neuroses" studied.

TABLE I.—THE CLINICAL MANIFESTATIONS OF AUTONOMIC IMBALANCE (A. L.)

No.	Age.	Sex.	Goiter noted at age of.	Duration of goiter, years.	Asthenia.	Loss of weight.	Palpitation.	Tachycardia.	Diarrhea.	Bulging eye.	Nervousness.	Dyspnea.	Gastric disturbance.	Menstrual disturbance.	Sweating.	Insomnia.	Irritability.	Headache.	Vasomotor irritability.	Tremor.	von Gräfe.	Exophthalmos.	Pigmentation.	Face oval.	Pulse.	Basal metabolism.	Neck shrink, months.	Consistency of goiter.	Bruit, etc.	Tonsils infected.	Sinus infected.	Apparent etiology of goiter.	Previous removal of thyroid. Result.
															PCB	ERT	Y																
8796	14	♀	?	?	○	○	○	○	○	○	+	○	○	○	○	○	○	○	○	○	○	○	○	:	140	:	1.25 cm 3 mos. Palp.	S.	○	○	○	Pub.	○
9197	36	♀	34	2	○	○	+	○	○	○	○	○	○	○	○	○	○	○	○	+	+	○	○	:	100	18		:	○	○	○	Pub.	Ectomy; x-ray.
8669	15	♀	14	3 mos.	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	:	160	.8	Palp.	:	○	○	○	Pub.	
8547	15	♀	14	1	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	:	130	7	Palp.	:	○	○	○	Pub.	
8741	17	♀	?	?	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	:	102	:	Palp.	:	○	○	○	Pub.	
8674	17	♀	15	2	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	:	86	:	Palp.	:	○	○	○	Pub.	
8720	16	♀	?	?	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	:	:	:	Palp.	:	○	○	○	Pub.	
9125	18	♀	15	24	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	:	96	:	Palp.	:	○	○	○	Pub.	Ops.
8031	15	♀	?	?	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	:	88	4	Palp.	:	○	○	○	Pub.	
8569	15	♀	13	2	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	:	:	:	9 cm. 8 mos.	:	○	○	○	Pub.	
8565	17	♀	16	1	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	:	:	:	:	F	○	○	○	Pub.	
9247	15	♀	15	2 mos.	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	:	96	:	7 cm.	S.	○	○	○	Pub.	
9157	18	♀	16	2	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	:	104	—6	6 mos.	F	○	○	○	Pub.	
8539	17	♀	?	?	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	:	:	:	6 cm.	S.	○	○	○	Pub.	
8984	16	♀	14	2	○	○	○	○	○	○	+	○	○	○	○	○	○	○	○	○	○	○	○	:	144	:	9 mos.	F	+	+	○	Pub.	
8636	14	♀	Birth	14	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	:	92	10	1.25 cm. 2 mos.	:	++	++	○	Pub.	
9079	14	♀	14	2 wks.	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	:	120	:	Palp. 2.5	:	+	+	○	Pub.	
8882	19	♀	19	2 mos.	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	:	:	:	3 mos.	F	++	++	○	Pub.	
9248	16	♀	14	2	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	:	120	4	Palp. 2.5	F	+○	+○	○	Pub.	
5273	13	♂	13	1 wk.	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	:	:	:	6 mos.	F	○	○	○	Pub.	
9190	14	♀	14	3 mos.	○	○	○	○	○	○	+	○	○	○	+	○	+	○	○	○	○	○	○	:	120	4	Palp.	S.	○	○	○	Pub.	
9159	19	♀	?	?	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	:	96	:	Palp.	:	○	○	○	Pub.	
8716	26	♀	16	10	○	+	○	○	○	○	+	○	○	○	○	○	○	○	○	○	○	○	○	:	112	:	Palp.	:	○	○	○	Pub.	
9202	32	♀	32	7 mos.	○	○	○	○	○	○	+	○	○	○	○	○	○	○	○	○	○	○	○	○	114	4	Palp.	:	○	○	○	Preg.	x-ray; electric.
9195	44	♀	?	?	○	○	○	○	○	○	+	○	○	○	○	○	○	○	○	○	○	○	○	○	104	16	Palp.	:	○	○	○	Preg.	
9124	30	♀	24	?	○	○	○	○	○	○	+	○	○	○	○	○	○	○	○	○	○	○	○	○	96		Palp.	:	○	○	○	Preg.	
															POS	F	FA																
															○	○	○																

| | | |

TABLE I.—THE CLINICAL MANIFESTATIONS OF AUTONOMIC IMBALANCE (A. I.)—*Continued.*

No.	Age.	Sex.	Goiter noted at age of.	Duration of goiter, years.	Asthenia.	Loss of weight.	Palpitation.	Tachycardia.	Diarrhea.	Bulging eye.	Nervousness.	Dyspnea.	Gastric disturbance.	Menstrual disturbance.	Sweating.	Insomnia.	Irritability.	Headache.	Vasomotor irritability.	Tremor.	von Gräfe.	Exophthalmos.	Pigmentation.	Face oval.	Pulse.	Basal metabolism.	Neck shrink, months.	Consistency of goiter.	Bruit, etc.	Tonsils infected.	Sinus infected.	Apparent etiology of goiter.	Previous removal of thyroid. Result.
8734	47	♀	44	3	○	○	○	○	○	○	+	○	○	○	○	○	○	○	○	○	○	○	○	○	...	..	5 cm. 3 mos.	○	○	+	○	○	
8158	31	♀	25	6	○	○	○	○	○	○	○	○	○	○	○	○	○	○	+	○	○	○	○	○	...	..	Palp.	○	○	○	○	○	Ectomy.
8493	28	♀	19	9	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	78	○	5 cm. 10 mos.	○	○	+	○	○	
5567	28	♂	26	2	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	...	..	Palp.	○	○	○	○	○	Ectomy.
8844	27	♀	20	7	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	...	..	Palp.	○	○	○	○	○	
8591	26	♀	26	3 mos.	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	...	..	Palp.	○	○	○	○	○	
8495	45	♀	?	?	+	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	...	..	Palp.	○	○	○	○	○	Ectomy.
9127	44	♀	38	6	+	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	96	..	Palp.	○	○	○	○	○	
9246	23	♀	?	?	+	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	...	..	Palp.	○	○	○	○	○	
8643	32	♀	32	3 mos.	+	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	...	..	Palp.	○	○	○	○	○	
5085	25	♂	?	?	+	○	○	○	+	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	...	..	Palp.	○	○	○	○	○	
8057	22	♀	?	?	+	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	112	9	Palp.	○	○	○	○	○	
8999	36	♀	?	?	+	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	...	..	Palp.	○	○	○	○	○	
5165	24	♂	?	?	+	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	...	..	Palp.	○	○	○	○	○	
8663	25	♀	25	6 wks.	+	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	...	..	Palp.	○	○	○	○	○	Ectomy.
8613	34	♀	23	11	+	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	70	2	....	○	○	○	○	○	
8730	40	♀	?	?	+	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	80	..	n. p.	○	○	○	○	○	
8498	38	♀	?	?	+	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	84	7	n. p.	○	○	○	○	○	
8740	27	♀	?	?	+	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	102	4	n. p.	○	○	○	○	○	
8540	38	♀	?	?	+	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	100	..	n. p.	○	○	○	○	○	Ectomy.
8449	26	♀	?	?	+	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	140	34	Palp.	○	○	○	○	○	*x*-ray.
8644	30	♀	?	?	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	132	..	Palp.	○	○	+	○	○	*X*-ray.
9078	20	♀	17	3	+	+	○	○	○	○	+	○	○	○	+	○	○	+	○	○	+	○	○	○	84	..	Palp.	○	○	+	+	○	

NOTE.—(1) Marked tachycardia in puberty group; (2) absence of relationship between pulse and B. M.; (3) absence of relationship between duration or type of thyroid enlargement and sympathomimetic symptoms; (4) preponderance of females; (5) asthenia and diarrhea more frequent in those over thirty-five and eye signs extremely infrequent; (6) eye signs and tremor comparatively frequent in those under thirty-five and asthenia and diarrhea infrequent; (7) no relationship between palpitation and pulse-rate; (8) the frequent occurrence of dyspnea and its independence of tachycardia, elevation of B. M. and cardiopulmonary lesions; (9) two instances of arrested exophthalmic goiter differing in no way except history of crisis from A. I.; (10) basal metabolism over plus 18 only once; (11) efficacy of iodides in reducing neck circumference; (12) efficacy of atropin in cardiac group; (13) frequent occurrence of infected tonsils; (14; infrequency of bruit; (15) exciting etiologic role of sex epochs, psychic insult and focal infection; (16) futility of operations on thyroid gland and roentgen-ray in reducing size of gland or symptoms; (17) practically every patient referred as exophthalmic goiter; (18) sympathomimetic symptoms independent of pulse and B. M., and may coexist with myxedema; (18) pressure symptoms from thyroid very rare.

10. *Tremor.* A coarse or fine tremor developed in 23 of these patients when the fingers were extended.

C. MANIFESTATIONS THAT MAY BE INFERRED TO BE SYMPATHOMIMETIC IN THAT THEY ARE FREQUENTLY PRESENT IN AUTONOMIC IMBALANCE AND ARE ACCENTUATED BY ADRENALIN. 1. *Nervousness.* Forty-nine women complained bitterly of "nervousness."

2. *Asthenia.* Asthenia was complained of by 30 patients. This symptom was rarely found in the puberty group but extremely common in the others.

3. *Goiter.* Seventy-two of the 86 patients had a definitely enlarged thyroid gland. The duration of the goiter varied between two weeks to thirty years, and neither the duration nor the size of the goiter bore any relation to the symptoms. There was no uniformity in the consistency of the gland; some were firm, others soft. In 2 patients a bruit was audible over the gland. The relation of the onset of the goiter to the sexual cycle, particularly puberty, was striking in many instances.

Every member of the puberty group (16) had undergone specific but futile treatment referable to the thyroid gland. Ten had been subjected to thyroidectomy; 1 had had two operations. Eight had received roentgen-ray exposures without shrinking the goiter or relieving the symptoms. The effect of small doses of iodine in diminishing the size of the goiter was most striking, even in long standing cases. The earliest change noted was a softening of the gland. The average shrinkage of the neck circumference was about 1 cm. a month.

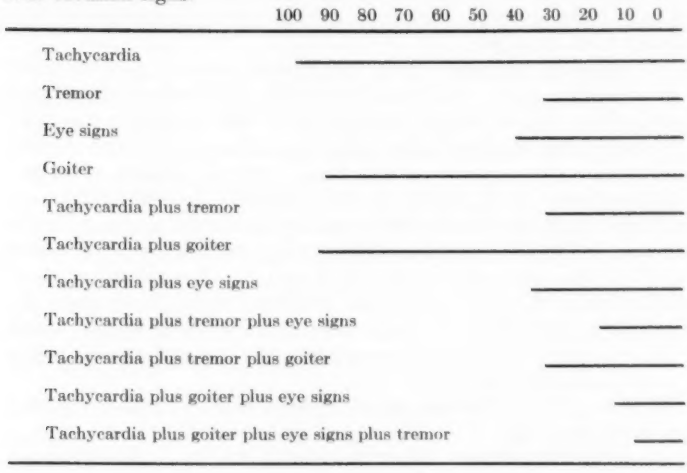
4. *Basal Metabolism.* Basal metabolism estimations were made on 31 of this group. Because of the fact that these patients were studied in the outpatient department it was necessary for them to come to the hospital before 8.30 A.M. Many had to travel great distances. Consequently a true basal rate was difficult to secure. The conditions under which the basal metabolism estimations were obtained made us regard +18 as within the normal range. Nevertheless, in but one woman (8449) was a striking elevation noted (+34). She was referred to the hospital and carefully studied, but a clinical diagnosis of Graves' syndrome could not consistently be made. Two other readings taken in the hospital were +4 and +8. In all but 5 of the other patients, the metabolism was below +10; the highest was +18.

The elevation of the metabolism bore no relation to the symptoms or to the pulse rate.

Associated Conditions. Many interesting conditions were observed associated with the autonomic imbalance. Concerning their relationship, data are insufficient to warrant definite conclusions. In 2 (8796, 8669) malnutrition appeared simultaneously with the goiter and the symptoms. Two girls presented the picture of Froehlich's syndrome (8674, 8636). One man had the hands of

typical acromegalia (5065). The cardiac arrhythmias and the psychoneuroses have already received comment. Four women displayed the clinical picture of myxedema (8592, 8598, 8613, 9127). Thyroidectomy was probably responsible in Case 8613, and this woman had a pulse rate of 70 and a basal metabolism of −2, with a persistence of all of her sympathomimetic symptoms. In all of these, thyroid extract caused a marked improvement. Two women (8632, 9126) gave a history that suggested Graves' syndrome; they were apparently now in the stage of arrest. Except for the crisis their histories differed in no essential respect from those of the other patients.

Correlation of Symptoms. The vast majority (84 per cent) of these patients presented both tachycardia and goiter; *i. e.*, two of the cardinal clinical symptoms of Graves' syndrome. There were 23 with tremor, and of these all but 5 had goiter and tachycardia. Thus 18 patients presented three of the four cardinal symptoms of Graves' syndrome. Twenty-six had either von Graefe's sign or exophthalmos; of these 9 had tremor and 6 had exophthalmos, tremor, tachycardia, and goiter (8716, 9202, 8598, 8860, 9126, 8476). Not one of these patients had a basal metabolism above +10; 1 (8598) had, in addition, some of the characteristics of myxedema. Fifty per cent of the entire group had three or more of the minor symptoms of Graves' syndrome and usually at least two of the four cardinal signs.


100 90 80 70 60 50 40 30 20 10 0
Tachycardia
Tremor
Eye signs
Goiter
Tachycardia plus tremor
Tachycardia plus goiter
Tachycardia plus eye signs
Tachycardia plus tremor plus eye signs
Tachycardia plus tremor plus goiter
Tachycardia plus goiter plus eye signs
Tachycardia plus goiter plus eye signs plus tremor

Sensitiveness to Drugs. In a few of these patients the responses to the subcutaneous injections of atropine and of adrenalin were determined. The incidence of reaction in individuals free from symptoms was first ascertained. Two groups of subjects were

chosen—second-year medical students at the College of Physicians and Surgeons, Columbia University, and convalescent medical and surgical patients at Mount Sinai Hospital. Reference to Table II shows that of the medical students 31 per cent responded to adrenalin and 22 per cent to atropine. None of these students had symptoms of imbalance. Table II shows also that of the hospital patients 30 per cent reacted to adrenalin and 22 per cent to atropine. It is evident, therefore, that sensitiveness to these drugs does not imply active autonomic imbalance, and in the article on Graves' syndrome[13] (No. III of the series) it will be shown that autonomic imbalance may exist without drug sensitiveness. We interpret drug sensitiveness in the absence of clinical symptoms of autonomic imbalance as evidence of a latent imbalance and are therefore attempting to keep these individuals under observation. The absence of drug reactions in the presence of clinical manifestations of autonomic imbalance is due to the fact that those particular structures on which the drugs act are in a state of normal irritability. Sensitiveness to adrenalin means nothing more or less than a lowering in the excitability threshold of the myoneural junction of the thoracico-lumbar division; increased reactivity to atropine, which paralyzes the myoneural junction, indicates an increased tonus of the entire bulbo-sacral system. The reactivity to these drugs is therefore no index of the state of the involuntary nervous system as a whole. In the vast majority of patients with autonomic imbalance sensitiveness to adrenalin or atropine is present; this sensitiveness suggests the type of autonomic imbalance. The sensitiveness is not necessarily universal and may be limited to one organ, so that an individual may have either a purely local or a general autonomic imbalance.

Sensitiveness to these drugs cannot therefore be taken as an absolute objective test for the presence of active autonomic imbalance. It is, however, extremely useful as an adjuvant in the diagnosis and together with the clinical impression may serve to corroborate a clinical suspicion. It is probably present as frequently in autonomic imbalance as in Graves' syndrome and is of no aid in this differential diagnosis. To us, these reactions have been of invaluable assistance in our conception of the disturbance and in the management of the patient.

Our technic has been greatly simplified. In order to obtain a basal pulse rate and pressure reading under the prevailing conditions, we first insert the needle into the subcutaneous tissues. The pulse rate and blood-pressure readings are then taken until a constant is obtained on several readings. The barrel of the hypodermic is then attached to the needle and the drug injected. For the adrenalin (0.5 cc) test the pulse rate is taken every minute and the blood-pressure as frequently as possible (two or three a minute) for the first ten minutes. If no reaction occurs after that time the test

is usually discontinued and reported negative. For the atropine test 1 mgm. of atropine sulphate is injected and the pulse rate counted every minute for twenty minutes in a negative test. In positive tests, the readings are discontinued at the fastigium.

Many interesting pharmacological data were obtained. The usual adrenalin response occurs within a few seconds and is ordinarily marked by a pressor followed by an accelerator response and

TABLE II.—THE RESPONSES TO THE SUBCUTANEOUS INJECTIONS OF ATROPIN AND ADRENALIN IN TWO GROUPS OF "NORMAL PERSONS" (MEDICAL STUDENTS AND CONVALESCENT PATIENTS).

NOTE.—No relation between adrenalin and atropin sensitiveness; no relation between subjective symptoms and objective findings; no relation between original pulse-rate or B. P. and extent of response.

Subjects.	Before adrenalin		General condition.	After adrenalin.		Subjective symptoms.	Atropin.	
	Pulse.	Bl. Pr.		Pulse.	Bl. Pr.		Before pulse.	After pulse.
E. Bessie	....	....	Medical student	....	....	Dry mouth	84*	100*
J. Besel	....	....	" "	....	....	.....	82*	112*
H. Bresky	....	....	" "	....	....	.....	84	78
de Merc	....	....	" "	....	....	.....	74*	90*
J. Dranit	....	....	" "	....	....	.....	72	72
H. Farnham	....	....	" "	....	....	.....	80	76
Frank	....	....	" "	....	....	.....	84	80
Goldin	....	....	" "	....	....	.....	76	76
Hansen	....	....	" "	....	....	.....	70	64
Lefk	....	....	" "	....	....	.....	84	72
MacDon	....	....	" "	....	....	.....	82	80
Milgrim	....	....	" " (asthma)	....	....	.....	66	58
Mulinos	....	....	Medical student	....	....	.....	60	54
G. Neuman	....	....	" "	....	....	.....	60	54
I. Reich	....	....	" "	....	....	.....	78	88
Rosenblatt	....	....	" "	....	....	.....	76	82
G. S. S.	....	....	Research Ass't.	....	....	.....	82*	106*
Talty	....	....	Medical student	....	....	.....	88	84
No. 111	....	....	" "	....	....	.....	90	82
Austrian	76	106	" "	78	106			
Bowen	68	114	" "	80	114	Slight tremor		
Chobat	78	122	" "	110*	156*	Faint; sweat; tremor; irregular respiration, cold		
Foland	80	124	" "	80	124			
Fordyce	80	118	" "	76	118	Pallor; nausea		
Griswold	72	124	" "	88*	156*	None		
H'horn	74	110	" "	108	128	Psychic		
Kohn	80	128	" "	80*	156*	Slight tremor; throb		
MacKie	72	116	" "	96*	160*	Headache; air hunger; tremor; pallor		
Monash	108	140	" "	134	160	Psychic (?)		
Murphy	....	....	" "	....	....	.....	68	52
L. Newman	102	....	" "	98	....	Tremor		
O'Brien	78	130	" "	76	138			
Peck	80	134	" "	86	130	Palpitation		
Schroeder	86	116	" "	80	120			
Shafton	80	110	" "	84	124			
Taintor	60	100	" "	110*	114*			
Twiss	64	110	" "	90*	156*			
Wall'st.	80	130	" "	90	134			
Wechsler	90	122	" "	98	130			
Weed	72	110	" "	84	112			
Yaswen	62	114	" "	78	118			
No. 111	90	124	" "	104*	158*	None		
M. Abr.	78	110	Bilateral hernia	88	120	.....	72	78
I. Altman	92	104	Post-pneumonia	120*	144*	Irregular tremor	90	94
R. Bagno	90	100	Mitral stenosis	96	104	Dyspnea; weakness	96	100
A. Bass	72	110	???? (Hysteria)	74	120	Weakness	72	66
A. Below	72	100	Salpingectomy; appendicectomy	100*	130*	Tremor; weakness	78	88
B. Berlin	60	110	Cancer of colon (?)	60	110	.....	60	66
I. Berman	84	120	Varicose veins	88	112	.....	84	74

Bookblat	....	....	Hernia	....	....	.....	84	90
Budofsky	78	114	Hernia	96*	130*	Tremor	78	72
Boerque	86	124	Intest. obstruct.	90	130	.....		
M. Cohen	88	110	Osteomyelitis	96*	130*	.....	96*	112*
Constant.	78	110	Contracture	84	116	.....	72	60
Davidof	60	100	Hyperacidity	72	104	.....	60	54
Finkelman	84	100	Mitral stenosis	108	104	Palpitation	78	84
Fleser	84	110	Hemorrhoids	96	116	.....	78	60
Freedman	60	110	Neuritis	60	110	.....	60	60
Goab	72	110	Post-pneumonia	72	110	.....		
Greenst.	84	112	Catarrhal jaundice	84	116	.....	84	88
Goldberg	96	124	Osteomyelitis	102	114	.....	96	104
Goldblat	72	104	Syphilis	76	108	.....	84	88
Gottlieb	78	120	Spondylitis	90	120	.....	80	72
Higgins	....	....	Bronchopneumonia	....	....	.....	72	76
Kaplan	60	114	Acute appendicitis	96*	144*	Palpitation arythmia	60	64
Kardish	96	116	Cyst of breast	100	120	.....	96	92
Katz	60	110	Ulcer of stomach (?)	60*	130*	None	60	64
Kaufman	....	....	Cancer of breast	....	....	.....	90*	132*
S. Kaufman	96	100	Cholecystectomy	102*	120*	.....	96*	114*
Kearns	104	112	Phlebitis	120*	150*	Dyspnea; palp. tremor	100	109
Klein	90	104	Osteomyelitis	120*	130*	Palpitation	98*	110*
Kupnisky	92	120	Hernia	96	126	.....	88	92
Kleiner	78	114	Fistula	90*	144*	None	78	74
Levison	60	106	Gastralgia	86*	148*	Palpitation, asthenia	64	66
Levitt	84	120	Rheum. fever	120*	140*	Palpitation, asthenia; tremor	78*	90*
Lischof	50	114	Post-pneu.	60	106	.....	50	56
Luder	66	100	Gastric sympt.	84	106	.....	72	66
Mandel	84	100	??	112*	124*	None	66*	86*
Marcus	72	110	Gastric neurosis ?	108*	136*	Epigastric pain; tremor	72	60
Masher	....	....	Hernia	....	....	.....	88	72
Matz	88	96	Pneumonia	96	100	.....	66*	84*
Maxod.	60	90	Arthritis	66	96	.....	68	60
McManus	58	120	Lacerations	76	110	Tremor	52	56
Newman	78	104	Calculus	70	108	.....	72	82
Newman	60	120	Hernia	64	126	.....	60	64
Perlonsk	84	100	Lipoma	96	110	.....	90	80
Peroker	92	98	Hermaphrodite	102	102	.....	84	92
Pestowitz	72	112	Acute app.	78	118	.....	66	72
Philips	84	124	Exploratory ops.	120*	166*	Palpitation; pallor; asthenia	72	84
Pikus	72	130	Pneumonia	118*	180*	Palpitation	72*	96*
Pressman	66	116	Tonsillitis	98	128	Tremor	72	66
Preist	96	110	Rheum. fever	100	124	Tremor	84*	96*
Patterman	96	110	Pregnancy	116	120	Tremor; asthenia	96	100
Riley	60	108	Gastric (?)	64	110	.....	60	60
Rubel	72	110	Breast tumor	76	116	.....	68	76
Sanders	64	94	Acute app.	90*	130*	Nervous tremor; sweat	66	72
Schatzman	....	....	Pneumonia	....	....	.....	84*	126*
Schier	72	124	Breast tumor	80	130	.....	68	60
Scott	92	104	Gastric ulcer	144*	116*	Palpitation; weak.	66*	96*
Simon	....	....	Empyema	....	....	.....	96*	116*
Schrenken	72	100	Pneumonia	78	112	.....	72	60
Skolnick	78	128	Gastric ?	92	140	.....	84	80
Slovak	84	130	???	92	130	.....	78*	96*
Siegel	84	160	Gastric ulcer	96*	174*	None	84*	108*
Suntlund	78	100	Pneumonia	84	100	.....	80	74
Sura	78	100	Gastric ?	100	110	Tremor	74	74
Wollner	72	104	Nephritis	74	110	.....	72	78
Winnitz	80	124	Cholelithiasis	84	128	.....	80	84
Wolofsky	90	104	Rheum. fever	96	108	.....	84	90
Yussman	90	140	Hernia	96	144	.....	84	90
Zifferbl.	106	108	Myositis (?)	118	112	.....	72*	112*

Recapitulation: Of 20 medical students, 4 react to atropin = 20 per cent.
Of 67 patients, 15 react to atropin = 22 per cent.
Of 87 total, 19 react to atropin = 22 – per cent.
Of 22 medical students, 7 react to adrenalin = 31 per cent.
Of 63 patients, 19 react to adrenalin = 30 per cent.
Of 85 total, 26 react to adrenalin = 30 per cent.
Asterisk indicates positive reactions.
Medical students tested by Drs. S. Hershfield and Hyman: patients by Dr. K. Wallach.

associated with subjective distress (precordial pain, sense of fulness, fear and an intense and alarming ashen-pallor). Tremor usually occurs later, after the vascular response has ceased. As atypical phenomena we have seen diphasic responses in a few instances (Chart I, A). In these the initial vasodilatation was present

followed by the familiar pressor response. We never obtained a pure dilatation. Again, we have seen a pressor response that was intense unassociated with an augmentor response (Chart II) and an acceleration unassociated with elevation of blood-pressure (Chart I, B). A delayed type of curve (Chart I, C) was noted a few times and in these, the reaction did not reach its height for twenty minutes. Corresponding to this "selective" action on the vascular system was variation in the subjective manifestations. There was no relationship between the subjective and objective reactions any more than the pressor and accelerator responses. An intense pressor or accelerator response may occur without subjective distress and subjective distress may be great without

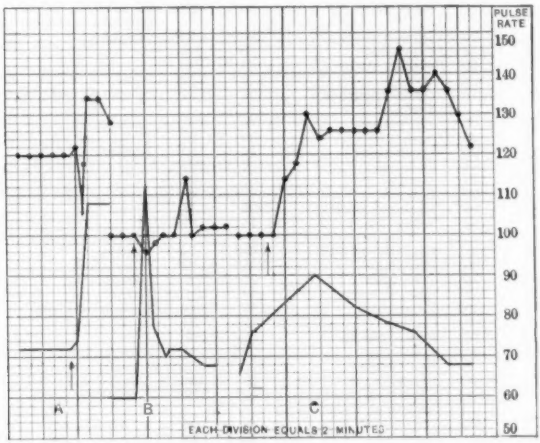


CHART I.—Dotted line is blood-pressure and plain line pulse rate. Arrow indicates time of injection. I—A, B, C and II are adrenalin and III an atropine reaction.

objective phenomena. The delay in the occurrence of tremor was constant. These selective types of reactions suggest an explanation for the variability of the clinical pictures in autonomic imbalance. For it must be evident that alterations may occur within the involuntary nervous system and may not be shared universally.

The atropine response was usually recorded as an initial pulse slowing (Chart III) occurring in the first four to eight minutes (due to vagus center stimulation), followed by a secondary acceleration occurring in from eight to twelve minutes and reaching a fastigium in about thirty minutes (due to peripheral paralysis). Aside from dryness of the mouth and flushing no subjective phenomena were noted and there was never any pressor response. The atropine "reversal" due to the central action was most closely studied and

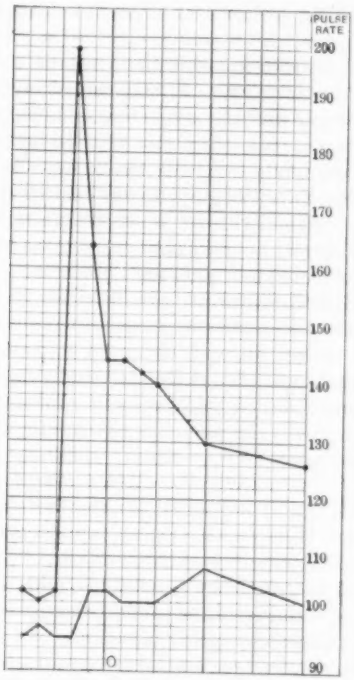


CHART II

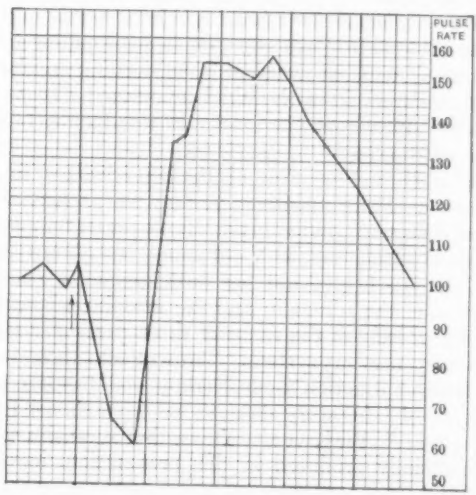


CHART III

an attempt made to utilize this effect therapeutically with some success.

There was no relation between the atropine and the adrenalin responses, between the types of response of one or the other or between any of these and the subjective or objective symptoms of the patients. Neither was there any relation between the presence of reaction and the intensity of the upset clinically.

Diagnosis. The most constant symptoms in these patients are tachycardia and goiter without fever or alteration in the basal metabolism. There is no difficulty in recognizing the syndrome.

The differentiation from Graves' syndrome cannot be made from any one clinical symptom. It has already been pointed out that tachycardia and goiter are present in practically all patients with autonomic imbalance, and that many have in addition tremor, eye-signs, and even all four of the cardinal symptoms of Graves' syndrome. None of our 86 patients had a constantly elevated basal metabolism, and this is the sole objective finding that differentiates autonomic imbalance from Graves' syndrome. However, the diagnosis can be made clinically. After seeing a certain number of these patients one is impressed by the fact that they differ in appearance from those with Graves' syndrome. Our attempts to express this difference in words have failed.

The exciting factor must be carefully sought, for the autonomic imbalance may be the result of some primary condition, such as tuberculosis, or a local pyogenic infection.

Autonomic imbalance is often diagnosed as a form of thyroid or adrenal disturbance; larval hyperthyroidism or formes frustes of exophthalmic goiter or suprarenal insufficiency (asystole). In view of the fact that we have been unable to satisfy ourselves that thyroxin or epinephrin plays any part in maintaining the involuntary nervous system, we consider it misleading to classify these patients as sufferers from thyroidal or adrenal disease.[9] This is important not only from the academic standpoint, but from the standpoint of therapy.

The utilization in diagnosis of the sensitiveness to drugs has been discussed. Drug sensitiveness may be present in about 25 per cent of "normal" individuals. It is present in about 80 to 90 per cent of individuals with autonomic imbalance and Graves' syndrome. It is a helpful but not pathognomonic reaction. The sites of action of the adrenalin and the atropine suggest that they are indicative merely of the tonus of those particular structures in the involuntary nervous system. To read into these reactions an index of thyroid function is misleading and based on erroneous interpretation of laboratory data, as we have shown in our work on the pithed cat.[10] We have also shown that adrenalin sensitiveness may be artificially produced in this preparation, independent of

thyroid function. There remains, therefore, no scientific basis for the utilization of the adrenalin test in the diagnosis of thyroid disease. Reliance on this test, as may be seen, would place many of these patients in the category of "exophthalmic goiter" and this in turn might mean subjection to a needless thyroidectomy. Too great emphasis cannot be placed on this point.

Management. Each patient usually comes for the relief of a single symptom. Unless the exciting cause of the imbalance can be removed, the management of these patients is extremely discouraging. When autonomic imbalance is associated with psychic insult much can be done by reassuring the patients and convincing them that their symptoms are not of serious import. When focal infections are present striking results sometimes follow local treatment. In the instances in which the imbalance is associated with the sexual epochs, the administration of gonadal extracts is of no benefit. The symptoms of general autonomic imbalance are most amenable to correction of general hygiene (mental and physical), and to physiological rest. The local symptoms, referable to the bulbo-sacral, are at times alleviated by atropine. If the symptoms are those of increased tonicity, atropine should be administered in large doses to secure the peripheral effects; if the symptoms are those of decreased tonus, atropine is indicated in such small doses that the centers are stimulated while the periphery remains unaffected. Where the manifestations originate in the thoracico-lumbar no specific remedy is available. Adrenalin is so transient in its action that it is useless; furthermore, if sensitiveness to adrenalin exists, the patient may be made extremely uncomfortable.

Course. Autonomic imbalance usually runs a long course. Occasionally it is transitory, as during the establishment of puberty, or when the exciting focus of infection can be removed. Where the exciting cause remains operative, the course is protracted, and even the best hygienic conditions afford no more than a temporary relief, and recurrences and exacerbations are the rule. These patients must b kept under constant observation. Only one patient developed a true Graves' syndrome with elevation of the basal metabolism while under observation. She was a girl of eighteen, and after tonsillectomy under local cocaine anesthesia developed a striking and severe crisis. These patients will be carefully followed during the next few years to learn whether they develop Graves' syndrome.

Conclusions. 1. A study of the clinical manifestations of autonomic imbalance is presented.

2. Such instability of the involuntary nervous system probably constitutes a diathesis.

3. Focal infection, psychic trauma and the sex epochs accentuate the syndrome.

4. The symptoms are strikingly similar to those in Graves' syndrome. Autonomic imbalance may coexist with myxedema.

5. Local manifestations in a single organ, such as the stomach or heart, may attract attention to the organ itself, instead of to the general disturbance of the involuntary nervous system.

6. Hyperplasia of the thyroid gland is a very frequent accompaniment of the syndrome. It is more likely secondary than causative.

7. There is never present in autonomic imbalance a distinct and continuous elevation of the basal metabolism. This serves as a crucial differential point from Graves' syndrome.

8. The recognition of clinical autonomic imbalance is simple. More important, however, is (1) the exclusion of Graves' syndrome, and (2) the determination of the exciting cause of the imbalance.

9. There are no scientific data that substantiate the participation of the ductless glands in the production of this syndrome.

10. While patients with autonomic imbalance usually are sensitive to either atropine or adrenalin, it is possible to have the syndrome without drug sensitiveness; also it is possible without active autonomic imbalance to have drug sensitiveness. The explanation of these facts on a pharmacological basis is recorded.

11. Clear-cut subgrouping of these patients into vagotonic and sympathicotonic cannot be made clinically until some definite information with regard to the tonus of the involuntary nervous system is forthcoming.

12. Autonomic imbalance can rarely be permanently arrested. Usually the symptoms may be alleviated, but the diathesis persists.

13. Hormone therapy is without foundation, and, practically, it is useless.

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THE SPONTANEOUS VARIABILITY OF BLOOD-PRESSURE AND THE EFFECTS OF DIET UPON HIGH BLOOD-PRESSURE, WITH SPECIAL REFERENCE TO SODIUM CHLORIDE.

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The Variability of Blood-pressure. The fact that blood-pressure varies a great deal in the same individual, not only from day to day, but from hour to hour and even from minute to minute, is freely acknowledged in all theoretical considerations of the subject, but is not generally made use of in the practical application of these matters to clinical observation or research. It is very necessary that any one who attempts to gauge the success of therapy applied to cases of hypertension by the sphygmomanometer, should be thoroughly familiar with the rise and fall of blood-pressure readings that apparently occur in a spontaneous fashion, but in reality are brought on by changes in the emotional state of the patient.

A citation of some of the authors who have noted this instability of blood-pressure may serve to indicate how important a factor it is. In 1900, Gumprecht[1] showed that the blood-pressure of laborers dropped with rest in bed during the first week's stay in a hospital; in 1 case the readings dropped from 195 to 125. In the same article this author notes how a student when watching blood-pressure determinations, upon himself, always registered 15 mm. higher than when he did not; after quarreling a rise of 30 to 40 points was common; a patient having a systolic blood-pressure of 170 had one of 202 after a successful hand at cards, and in another the figure rose from 156 to 172 on being amused and laughing. Rolleston[2] finds that nervous influences may constrict the blood-vessels and bring about rapid changes in the blood-pressure. Schrumpf and Zabel[3] in various publications come to the conclusion that blood-pressure is very variable; that psychic causes, thought of good food, fear of pain, etc., are all likely to bring it about; that the nervous, neurasthenic type is more subject to such changes in the arterial tension than the placid individual, and that in normal persons the systolic pressure only varies, while in the arterio-sclerotic subject the diastolic fluctuates as much as the systolic. Hecht[4] showed that a low diet associated with physical and mental

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[3] Deutsch. med. Wchnschr., 1910, **26**, 2385. Schrumpf and Zabel: München. med. Wchnschr., 1911, **58**, 1952. Zabel: München. med. Wchnschr., 1910, **57**, 2278.
[4] Ztschr. f. klin. Med., 1912, **76**, 87.

rest reduced hypertension; this view has been endorsed by Janeway.[5] The two last observations indicate the difficulty that any students of this subject encounter. It is impossible to be certain which factor diminished the hypertension, the low diet or the nervous relaxation; it is obviously necessary that in any conclusive clinical observations the psychic elements must first be eliminated before any further data are obtained. Janeway also accentuated the variability of blood-pressure from hour to hour. Oliver[6] claimed rest to be an essential factor in the treatment of hypertension. Maloney and Sorapure,[7] and later Grossman[8] showed how relaxation brought about by breathing exercises and passive motion lowered the blood-pressure; they believe that by these measures the psychic influences resulting in vasomotor stimulation and consequent increase in blood-pressure are done away with. In one of their cases the systolic pressure dropped from 215 to 154. Tixier[9] made the interesting observation that it was rare for blood-pressure readings to remain stationary as long as five minutes. O'Hare[10] found that in most instances, though not in every one, blood-pressure fell during rest; within five to seventy minutes the systolic drop was as high as 46 mm. of mercury and the diastolic 18; excitement in his experience always caused a sharp rise in systolic pressure (as high as 52 mm. of mercury) and a more moderate rise in diastolic pressure (as high as 24 mm.). The most recent effort in this field is that of Boas,[11] who duplicated O'Hare's results and in addition showed how the blood-pressure varied in normal individuals and was particularly prone to fluctuate in those cases described as neurocirculatory asthenia.

The series of observations presented in Table I bears out the contentions of the investigators cited above. These patients were studied at the Vanderbilt Clinic, Outpatient Department; the blood-pressure was read when the subject lay down and subsequently at frequent intervals until it was evident that no further drop in pressure would follow. In all probability these results are less striking than would have been the case if the surroundings had been more conducive to the allayment of physical and mental unrest, since the patients reclined on a rather hard examining table and in most instances must have been more or less annoyed by the coming and going of many persons in the same room. It may be noted that the fall in systolic pressure was usually more marked than in the diastolic, that it occurred in nearly every instance but that at times the change was negligible and occasionally even a rise was present. From the therapeutic point of view it is worth noting that the greatest drop in pressure usually manifested itself well

[5] Am. Jour. Med. Sci., 1913, **145**, 25.
[6] Lancet, 1907, **1**, 1346.
[7] New York Med. Jour., 1914, **99**, 1021.
[8] Ibid., 1905, **102**, 645.
[9] Arch. d. mal. d. cœur, 1919, **12**, 337.
[10] Am. Jour. Med. Sci., 1920, **159**, 373.
[11] Medical Clinics of North America, 1920, **4**, 257.

TABLE I.—CHANGES IN BLOOD-PRESSURE OCCURRING IN THE RECUMBENT POSITION. EACH OBSERVATION WAS CONTINUED UNTIL THE BLOOD-PRESSURE CEASED TO FALL. THE MINIMAL BLOOD-PRESSURE AFTER LYING DOWN IN EACH CASE IS RECORDED IN THE TABLE. IN NEARLY EVERY INSTANCE THE BLOOD-PRESSURE READINGS WERE KEPT UP FOR A CONSIDERABLE PERIOD AFTER THE MINIMAL BLOOD-PRESSURES NOTED ABOVE WERE OBTAINED. THE RESULTS ARE CHARTED IN ORDER, ACCORDING TO THE DROP IN SYSTOLIC BLOOD-PRESSURE.

On lying down.		Lowest noted.		Fall.		Interval minutes.
Systolic.	Diastolic.	Systolic.	Diastolic.	Systolic.	Diastolic.	
244	126	200	96	44	30	10
230	106	188	92	42	14	18
250	120	210	108	40	12	10
215	120	176	115	39	5	90
228	126	190	116	38	10	8
192	104	156	96	36	8	24
280	136	250	122	30	14	30
265	110	235	100	30	10	18
170	104	140	98	30	6	35
184	90	154	88	30	2	15
220	98	190	110	30	12	60
226	102	198	102	28	0	20
226	128	200	118	26	10	12
162	94	136	92	26	2	7
178	100	153	96	25	4	35
220	110	196	120	24	+10	16
202	104	178	94	24	10	6
158	100	135	90	23	10	10
136	84	118	80	18	4	16
212	110	194	114	18	+ 4	17
234	134	218	120	16	14	21
210	104	194	106	16	+ 2	14
220	120	204	118	16	2	18
190	105	175	96	15	9	23
158	94	144	92	14	2	7
200	110	186	108	14	2	15
210	110	196	108	14	2	25
136	66	122	68	14	+ 2	20
140	90	126	85	14	5	38
198	?	184	?	14	?	29
232	132	218	128	14	4	34
160	106	148	108	12	+ 2	24
180	95	168	90	12	5	26
120	75	110	70	10	5	18
200	130	190	126	10	4	3
170	95	160	94	10	1	21
182	115	172	108	10	7	23
166	110	156	110	10	0	19
194	96	185	85	9	11	68
204	110	196	108	8	2	10
216	128	210	126	6	2	12
225	94	230	92	5	2	15
158	98	154	104	4	+ 6	22
156	108	154	106	2	2	33
150	100	150	100	0	0	17
120	84	122	88	+ 2	+ 4	36
126	84	128	88	+ 2	+ 4	11
210	120	214	124	+ 4	+ 4	25
245	140	260	140	+15	0	31

within half an hour, which shows that the customary short nap or rest after meals may have far-reaching results. It is important in this connection to appreciate the fact that subsequent blood-pressure readings, when the sitting or upright position was resumed, often did not return to the initial level of arterial tension, but remained lower for a considerable period.

A very remarkable picture of variations in blood-pressure effected by emotional stimuli is given in Table VII. Every time this patient conversed or was disturbed the blood-pressure rose, only to drop again in a few minutes when the emotional phase had passed away. His heart and arteries were apparently the play-things of his nervous system. Two instances are particularly noteworthy, that on August 11, when the blood-pressure was at a level of 242/116 while he was relating an unpleasant incident, whereas five minutes later the considerably lower reading of 194/114 was obtained, and that on August 20, when the same high systolic tension was again reached (242/120) as a result of the death of the patient in the neighboring bed.

It is perfectly evident from all these data and quotations that very prolonged control observations are necessary before the true blood-pressure (Tixier's "residual blood-pressure") in any case can be determined, and furthermore that the conditions under which the effect of diet, drugs or physical measures are judged, as to their therapeutic value, must be adjusted with scrupulous care.

The mechanism by which these abrupt changes in blood-pressure are brought about is not entirely clear. Cannon[12] states, and this reflects the consensus of opinion, that the main factors determining the degree of arterial pressure are: (1) The energy of the heart as measured by the volume of blood pumped into the arterial system within a given time, and (2) the degree of resistance present in the terminal part of the arterial system. Other considerations appear to be of minor importance. If the individual cardiac contraction becomes quicker and more powerful, though the volume of blood put out with each beat is unchanged, it is obvious that the systolic pressure will rise and that the diastolic will remain stationary; if the peripheral arteries contract and the resistance they present to the blood flow becomes increased, both the systolic and diastolic pressure will be elevated. A corresponding drop in systolic and diastolic pressures will occur if each heart beat becomes prolonged or less forceful and if the arterioles relax. In the blood-pressure changes that occur with rest or emotional stimuli it is probable that both these factors are concerned. It is certain that in most instances the pulse rate does not change and therefore an increased systolic pressure without an augmented diastolic pressure must be due to the increased speed and force of the individual heart beat; if, as

[12] Boston Med. and Surg. Jour., 1911, **165**, 672.

might be assumed, the total volume of blood put out per beat would be raised and the quantity of blood in the arterial system increased, then the diastolic pressure would rise as well. This is, however, improbable and it is much more reasonable to suppose that when the diastolic pressure does rise there is a contraction of the smaller arterioles. It is only natural to suppose that nerve stimuli, brought on by various emotional phases, influence both the heart action and the tone of the smaller bloodvessels so as to bring about the marked variations in blood-pressure which are of such common occurrence and of such great clinical importance.

The Effect of Proteins on Blood-pressure. Recently the results obtained by one of the authors in attempting to modify blood-pressure by protein feeding were published.[13] It is not necessary to reprint these experiments in detail and only a few facts necessary to round out the complete picture as to the relation of diet to blood-pressure will be alluded to.

There is a general impression abroad that proteins in the diet have a tendency to increase arterial tension. It is difficult to find very much carefully gathered evidence to support this contention. Goodall[14] found that in cases of chronic interstitial nephritis the blood-pressure dropped while the patients were taking a low protein diet. Most of the other publications advocating this as a fact are based upon general impressions and not upon properly obtained clinical data.

Recently Squier and Newburgh[15] came to the conclusion that "high protein diet over a short period had no effect on the blood-pressure." Their study included cases of essential hypertension as well as of nephritis. The amounts of protein given these patients were high, well over 150 gm. per day. As the result of the forced protein diet, signs of renal irritation appeared but the blood-pressure remained unchanged. Similar findings in regard to blood-pressure have been reported by Strouse[16] and by Mosenthal.[17]

The purins derived from proteins can not be held responsible for the production of an increased blood-pressure. In this regard possibly it is most conclusive to quote the words of Sir Clifford Allbutt:[18] "Again and again I have placed high-pressure patients on purin-free diets, or on vegetarian diet with cheese, milk and eggs, with no appreciable reduction of blood-pressure within such limit of weeks as to satisfy the conditions of an experiment."

Another phase of the problem of the relation of protein feeding to hypertension has been definitely set aside by the practice of

[13] Mosenthal, H.: Am. Jour. Med. Sci., 1920, **160**, 808.
[14] Boston Med. and Surg. Jour., 1913, **168**, 760.
[15] Arch. Int. Med., 1921, **18**, 1.
[16] Med. Clin. North America, 1921, **5**, 229.
[17] Am. Jour. Med. Sci., 1920, **160**, 808.
[18] Diseases of the Arteries including Angina Pectoris, 1915, **2**, 88.

modern blood chemistry. It was formerly believed that the retention of nitrogenous substances might be responsible for the raised arterial pressure. The experience of everyone practising this branch of medicine is that this idea is incorrect. Recently Williams[19] has again called attention to the fact that, "The height of the blood-pressure bears no relationship to the amount of non-protein nitrogen substances in the blood."

As far as the specific influence of proteins on blood-pressure is concerned there is only one refuge left for those who still believe in this theory and that is the possibility of the production of toxic materials from protein foods within the organism and a consequent pressor action of such substances. The idea that this is a probable explanation of high blood-pressure is widespread. However, there is nothing but circumstantial evidence to favor it; there are no proofs at hand which adequately demonstrate the value of colon irrigations or the control of the intestinal flora in various ways.

The Effect of Carbohydrates on Blood-pressure. It has always been taken for granted that carbohydrates play no role in influencing blood-pressure. It is certainly true that usually neither the amount of starchy food ingested nor the level of the blood sugar apparently change the blood-pressure in any way. On the other hand the liability of cases of diabetes mellitus to develop hypertension is well known. There may be other factors than the disturbed sugar metabolism responsible for this tendency to increased blood-pressure but the coincidence is at least suggestive. Occasionally instances are met with in which an excessive starch intake may either directly or indirectly be the cause of a rise in arterial tension. In certain instances the reduction of the starch intake leads to a definite lowering of the blood-pressure. Thus in a patient fifty-six years old, weighing 215 pounds with a blood sugar of 0.160, who ate a great deal more than his share, the blood-pressure dropped from 146/88 to 112/72 when the carbohydrates in the food were moderately curtailed. The weight at the same time diminished by 25 pounds. It is possible that the loss in weight, remedying of some dyspeptic symptoms or other influence may have been the cause of the fall in arterial tension. Such cases are not common, but they do exist. Dr. W. W. Herrick informs us that he has had two similar ones in whom the change in the level of hypertension was much more marked than in the patient detailed above. One of the present food fads is to avoid meats and to eat starch *ad libitum*. When these precepts are followed without discrimination hypertension, as well as obesity, appear to be among the possible penalties entailed.

The Effect of Sodium Chloride on Blood-pressure. The relation between sodium chloride and hypertension has been urged for

[19] Arch. Int. Med., 1921, **27**, 748.

some time. It is of interest to follow this subject in chronological sequence. In 1904 Ambard and Beaujard[20] claimed that there was a direct relation between retention of sodium chloride and the level of arterial tension. In 8 cases of nephritis studied by them 6 cases conformed to their theory and 2 did not. These 2 exceptions are notable: In the first no rise in blood-pressure occurred in spite of a retention of 60 gm. of salt and an accumulation of 5 kg. of edematous fluid; in the second the blood-pressure rose in spite of the elimination of large amounts of previously retained salt. Subsequently Ambard[21] reiterated his views and defined them a little more closely by expressing the belief that all hypertension is due to retention of sodium chloride and that every case of permanently increased blood-pressure is due to a nephritis. Today when it is a firmly established fact that a permanent rise in arterial pressure is very often not associated with a nephritis, this contention loses much of its force. Combe[22] quotes an interesting observation of Castaigne, that injections of sodium chloride may produce fatal uremia in "chronic atrophic nephritis;" Munk[23] made note of a somewhat similar instance after the administration of a rather large dose of salt. The authors had untoward symptoms occur in a case of nephritis with marked impairment of renal function after a 10 gm. dose of sodium chloride. However, in patients in whom kidney activity was normal, salt in this amount produced no manifestation (with the possible exception of nausea) whatsoever. These observations are set forth in subsequent tables. It is probably to this type of hypertensive disease, associated with marked nephritis, that Allen[24] refers when he remarks that if certain patients with a pressure of 200 received salt there would be fireworks. It must be borne in mind, however, that as shown in the present tables, 10 gm. of salt may be given without fear of harming the patient, provided the hypertension is an essential hypertension, not exhibiting any noteworthy secondary changes or complications.

Loeb,[25] in regard to this problem, makes the obvious but very significant statement that those forms of nephritis—the parenchymatous—that are characterized by a retention of sodium chloride, do not as a rule have a high blood-pressure. Bergouignan and Fiesniger[26] reported one patient who retained salt without a parallel holding back of water, during which period the blood-pressure remained unchanged, while in another instance with salt retention and edema the blood-pressure rose. Bayer[27] reported 6 cases of arteriosclerosis some of which showed a marked increase

[20] Arch. gén. de méd., 1904, **50**, 520.
[21] Thèse pour le Doctorat en Médicine. Semaine méd., 1906, **26**, 361.
[22] Monatschr. f. Kinderh., 1905, **4**, 13, 82.
[23] Pathologie und Klinik der Nephrosen, Nephritiden und Schrumpfnieren, 1918.
[24] Tr. Am. Assn. Phys., 1920, **25**, 76.
[25] Deutsch. Arch. f. klin. Med., 1905, **85**, 348.
[26] Bull. et mém. Soc. méd. d. hôp., 1906, **23**, 425.
[27] Arch. f. exper. Path. u. Pharmakol., 1907, **57**, 162.

in arterial blood-pressure on a high salt diet, whereas others gave evidence of little or none.

Brodzki[28] could produce no increase in blood-pressure with salt in either the experimental uranium nephritis of dogs or the cantharidin nephritis of rabbits. Lowenstein[29] was unable to note any relation of sodium chloride to blood-pressure in 4 carefully observed cases. In one patient the arterial tension diminished in spite of the retention of 50 gm. of salt within a few days. In a general article without definite evidence Oliver expresses the opinion that sodium chloride raises blood-pressure. As the result of the "Karlsbad Cure," in the course of which considerable saline water is taken, Ritter[30] noted his results as follows:

57 cases	Blood-pressure lowered
4 cases	Blood-pressure constant
17 cases	Blood-pressure raised

Allbutt's[31] opinion on one phase of this subject is as follows: "I have found that to cut out salt from the diet of healthy persons for a few days produces no changes of pressure."

Allen,[32] in 1920, made very strong claims for the specific relation between salt and arterial tension. He believes that pure hypertension is essentially a salt nephritis and that the apparent efficiency of salt excretion is purchased at the price of abnormally high blood salt and blood-pressure. The blood-pressure did not vary in direct proportion to the salt concentration of the plasma in all the cases submitted by Allen. This may be due in part to the fact that the sodium chloride was determined in the plasma and not in the whole blood, and in part that the apparently spontaneous fluctuations in blood-pressure brought on by emotional states were not sufficiently controlled. (On standing there is an increase of sodium chloride in the plasma brought about by the passage of carbon dioxide from the plasma to the blood.—Myers, and Myers and Short[33].) These theories concerning the relationship of salt, kidney function and blood-pressure are much like those of Ambard and his associates expressed about fifteen years ago. In one of Allen's cases the blood-pressure rose from 200/100 to 266/110 after the administration of 10 gm. of salt and in another it increased from 215/130 to 254/120 on forcing water. This preliminary report has been the subject of much discussion and there have been several brief comments upon it. McLester[34] failed to reduce the blood-

[28] Berl. klin. Wchnschr., 1906, **43**, 906; Deutsch. Arch. f. klin. Med., 1908, **93**, 310.
[29] Arch. f. exper. Path. u. Pharmakol., 1907, **57**, 137.
[30] Deutsch. Arch. f. klin. Med., 1910, **100**, 11.
[31] Diseases of the Arteries including Angina Pectoris, 1915.
[32] Jour. Am. Med. Assn., 1920, **74**, 652.
[33] Practical Chemical Analysis of Blood; Jour. Biol. Chem., 1920, **44**, 47.
[34] Jour. Am. Med. Assn., 1921, **77**, 88.

pressure in nephritis by limitation of the sodium chloride intake. A patient was given 10 gm. of salt every day for ten days by Strouse[35] and the blood-pressure dropped from 260/150 to 200/100.

Christian[36] quotes the work of his colleague O'Hare[37] on 46 patients showing that an increase of blood chlorides occurs in direct proportion as renal insufficiency develops; the blood-pressure apparently was higher in those cases with a low blood chloride than in those with a high. In anemia the blood chlorides rise considerably although the blood-pressure remains constant or diminishes.

In Table II the blood chloride findings are given for 26 patients whose systolic blood-pressure is above 200 mm. of mercury. If we regard 500 mg. sodium chloride per 100 cc of whole blood as the usual upper limit of normal[38] it is seen that in Table II only 2 out of the 26 cases of hypertension are abnormally high. This observation bears out some of the facts quoted to the effect that hypertension and an increased blood chloride do not go hand in hand.

If this problem is approached from another angle it is found that cases in which the blood chlorides are high are not necessarily accompanied by an increased blood-pressure (Table III).

From the above quotations and data it becomes clear that an increase in the blood chlorides does not produce a rise in blood-pressure.

A few experiments were carried out to determine the effect of moderate doses of sodium chloride on patients suffering with hypertension. Those with marked renal insufficiency were avoided, since in them, as previously mentioned, there are untoward and even dangerous manifestations when the body is suddenly flooded with salt in this way. The patients were kept in bed for a period of days and frequent blood-pressure readings were made. It is only by these means that a true control estimate of the arterial tension can be obtained. After the spontaneous variations characteristic of each case of essential hypertension had been recorded, 10 gm. of sodium chloride were given by mouth or through a small stomach tube (to avoid the taste of the bitter solution) and frequent blood-pressure readings were made subsequently. The individual experiments are given in Tables IV, V, VI, VII, VIII and IX.

In Tables IV to IX the individual reactions may be studied in detail. For purposes of discussion only a summary of these observations, as given in Table X, will be alluded to.

[35] Med. Clin. North America, 1921, **5**, 229.
[36] New York State Jour. Med., 1921, **21**, 292.
[37] Proc. Am. Soc. Clin. Investigat., 1921, p. 6.
[38] Practical Chemical Analysis of Blood, 1921, p. 91.

TABLE II.—BLOOD-PRESSURE AND BLOOD SODIUM CHLORIDE IN 26 SUCCESSIVE CASES OF HYPERTENSION (BLOOD-PRESSURE OF 200 OR HIGHER) ARRANGED IN ORDER OF THE LEVEL OF THE BLOOD SODIUM CHLORIDE. IN ONLY A VERY FEW CASES IS THE BLOOD SODIUM CHLORIDE ABOVE NORMAL.

Case.	Blood-pressure.		NaCl mg. per 100 cc whole blood.
	Systolic.	Diastolic.	
I	226	90	627
II	208	94	557
III	214	136	500
IV	200	82	500
V	212	130	500
VI	242	180	495
VII	202	114	495
VIII	224	120	494
IX	224	106	494
X	206	126	488
XI	212	130	488
XII	260	158	488
XIII	235	125	486
XIV	216	132	478
XV	210	114	478
XVI	320	160	474
XVII	210	116	474
XVIII	246	120	462
XIX	240	145	450
XX	250	140	450
XXI	224	140	445
XXII	224	136	429
XXIII	204	128	429
XXIV	224	136	429
XXV	204	126	410
XXVI	265	168	410

TABLE III.—CASES WITH NORMAL BLOOD-PRESSURE AND AN INCREASE OF THE BLOOD CHLORIDES.

Diagnosis.	Blood-pressure.		NaCl mg. per 100. cc whole blood.
	Systolic.	Diastolic.	
Secondary anemia	105	52	660
Parenchymatous nephritis	98	80	625
Carcinoma kidney	120	68	622
Normal	120	71	597
Carcinoma rectum	140	84	588
Cholecystitis	110	80	567
Normal	128	94	561
Obesity	135	85	553
Carcinomatosis	104	78	550
Pernicious anemia	130	70	550
Normal	120	75	540
Normal	112	80	539
Cyclic vomiting	125	80	539
Carcinoma stomach	108	82	538
Diabetes mellitus	108	74	532

The "spontaneous" variations of the blood-pressure occurring during a period of a few days before the test substance is given are shown in Table X (under heading of control blood-pressure).

At the risk of repeating some of the statements made in the introductory section of this paper it is desirable to emphasize the necessity of making these prolonged control observations before plunging into any experiments that are supposed to yield results concerning blood-pressure. The variations in these cases are much more marked than they were in the individuals whose blood-pressure was recorded for short periods of rest only (Table I).

TABLE IV.—E. F., FEMALE, AGED FORTY-EIGHT YEARS. ESSENTIAL HYPERTENSION, RENAL FUNCTION UNIMPAIRED. MARKED "SPONTANEOUS VARIATIONS" IN BLOOD-PRESSURE. GLASS OF COLORED WATER PRODUCES SLIGHT INCREASE IN BLOOD-PRESSURE, COMPARABLE TO THE EFFECT OF 10 GM. OF SALT IN SOME OTHER CASES. A LOW SALT DIET DOES NOT DIMINISH THE BLOOD-PRESSURE.

Date, 1921.	NaCl 24 hrs. urine, gm.	Diet.	Blood-pressure.			NaCl whole blood, mg. per 100 cc.	Remarks.
			Time.	Systolic.	Diastolic.		
Jan. 29	..	Regular	1.04 P.M.	226	108		
			1.07	210	106		
			1.09	200	106		
			1.10	184	106		
			1.11	182	106		
31	8.10	Regular	1.13 P.M.	224	106	494	
			1.16	228	110		
			1.21	214	106		
			1.23	206	106		
			1.25	192	102		
			1.26	198	106		
			5.53	236	114		
			5.57	230	112		
			5.58	220	110		
			5.59	214	110		
			6.00	214	110		
Feb. 1–4	3.50	Regular	....	230	116	....	Maximum for period.
	2.24	....	....	180	102	....	Minimum for period (12 blood-pressure readings).
4–15	3.20	"Salt-free"	....	238	120	....	Maximum for period.
	0.78	....	....	160	90	....	Minimum for period.
	1.52	....	....	....	....	....	Average for period (42 blood-pressure readings; 7 NaCl determinations).
15	1.60	"Salt-free"	9.08 A.M.	200	96	....	Felt better than usual.
			9.09	190	100		
			9.12	176	100		
			9.16	184	104		
			10.10	....	....	....	Glass of pink colored water taken by mouth; patient told that it might increase blood-pressure temporarily.
			10.18	208	98		
			10.20	188	96		
			10.52	190	104	....	Felt distressed, headache.
			10.54	190	100		
			10.57	192	104		
			12.40 P.M.	214	106	....	Felt worse, headache increased; "hot flashes."
			12.43	190	100		
			7.32	210	110		
			7.35	210	110		
			7.37	204	110		
			7.45	190	110		
16–28	5.00	....	....	233	120	....	Maximum for period.
	0.68	....	....	184	102	....	Minimum for period.
	1.92	....	....	....	....	....	Average for period (10 NaCl determinations).

TABLE V.—A. K., FEMALE, AGED FORTY YEARS. ESSENTIAL HYPERTENSION, SLIGHT DEGREE OF AORTIC INSUFFICIENCY (NO SIGNS OF LUES, WASSERMANN REACTION NEGATIVE), RENAL FUNCTION UNIMPAIRED. MODERATE "SPONTANEOUS VARIATIONS" IN BLOOD-PRESSURE. MODERATE RISE IN BLOOD-PRESSURE FOLLOWING THE INGESTION OF 7 GM. OF SODIUM CHLORIDE; THE MARKED RISE IMMEDIATELY AFTER THE TAKING OF THE SALT MAY BE ATTRIBUTED TO THE ATTENDANT NAUSEA.

Date, 1920.	NaCl 24 hrs. urine, gm.	Diet.	Blood-pressure.			NaCl whole blood, mg. per 100 cc.	Remarks.
			Time.	Systolic.	Diastolic.		
Aug. 10	....	Regular	....	200	90	....	On admission to hospital.
11–29	7.74	"Salt-free"	....	212	96	485	Maximum for period.
	1.00	....	....	170	84	467	Minimum for period.
	3.51	....	....	....	....	....	Average for period (19 blood-pressure readings; 8 urine NaCl and 2 blood NaCl determinations).
30	3.10	"Salt-free"	3.30 P.M.	198	92	....	Sitting up.
			3.35	190	88	....	Reclining and resting.
			3.40	188	96	....	Reclining and resting.
			3.42	182	96	....	Reclining and resting.
			3.44	182	96	....	Reclining and resting.
31	2.90	"Salt-free"	10.15 A.M.	192	88	....	After sitting up.
			10.20	180	88	....	Reclining and resting.
			10.25	174	92	....	Reclining and resting.
Sept. 1	....	"Salt-free"	10.30 A.M.	220	96	....	Sitting up.
			10.33	198	96	....	Reclining and resting.
			10.40	190	94	....	Reclining and resting.
			10.42	186	90	....	Reclining and resting.
			10.44	184	90	....	Reclining and resting.
2	2.50	"Salt-free"	1.30 P.M.	212	94	....	Sitting up and conversing.
			1.35	178	92	....	Reclining and resting.
			1.37	180	92	....	Reclining and resting.
3	2.00	"Salt-free"	10.30 A.M.	200	82	500	Sitting up.
			10.32	220	98	....	After conversing.
			10.37	204	96	....	Reclining and resting.
			1.30 P.M.	208	90	....	Sitting up.
			1.35	180	90	....	Reclining and resting.
			1.40	178	90	....	Reclining and resting.
			3.30	204	88	....	After walking about ward.
			3.35	176	88	....	After resting five minutes.
			3.40	172	74	....	After resting ten minutes.
4	1.47	"Salt-free"	1.00 P.M.	214	90	....	After walking about ward.
			1.05	182	86	....	After resting five minutes.
			1.10	164	84	....	After resting ten minutes.
			4.30	206	86	....	After walking about ward.
			4.40	194	90	....	After resting ten minutes.
			4.42	192	88	....	After resting twelve min.
5	3.70	"Salt-free"	11.30 A.M.	200	86	....	After resting five minutes.
			11.35	178	90	....	After resting ten minutes.
			11.40	180	84	....	After resting fifteen min.
				205	90	....	After walking about ward.
				195	87	....	After resting five minutes.
				190	85	....	After resting ten minutes.
6	2.24	"Salt-free"	2.00 P.M.	190	90	....	Reclining and resting.
			2.05	179	86	....	
			2.10	178	86		
7	....	....	9.30 A.M.	206	100	....	Reclining and resting.
				190	98	....	
				196	96		
		....	9.45	....	....	....	7 gm. NaCl in 135 cc water taken by mouth; very disagreeable to patient.
			9.58	266	126	....	Patient somewhat nauseated.
	0.97	....	10.00	....	....	....	Output for two hours.
			10.03	247	106		
			10.10	226	110		
			10.14	232	114		
			10.17	232	112		
			10.18	238	114	....	Still nauseated.
			11.32	214	102		

Date, 1921.	NaCl 24 hrs. urine, gm.	Diet.	Blood-pressure.			NaCl whole blood, mg. per 100 cc.	Remarks.
			Time.	Systolic.	Diastolic.		
			11.34	214	104		
			11.43	214	98		
			11.54	....	....	497	
	0.75	....	12.00 M.	....	....	....	Output for two hours.
			1.13 P.M.	216	87		
			1.15	190	88		
			1.18	189	92		
			1.20	190	92		
			1.23	190	94		
			1.30	....	....	494	
	2.75	....	1.50	....	....	....	Output for one hour fifty minutes.
			2.25	214	94	....	One visitor (daughter).
			3.00	220	94		
			3.05	220	90		
			3.06	220	94		
			3.09	218	100	....	Visitor left.
			3.15	....	....	490	
			4.00	190	90		
			4.03	200	94		
			4.10	188	88		
			4.17	198	94		
			4.23	190	94		
			5.38	210	94		
			5.41	204	92		
			5.47	210	96		
			5.55	....	....	475	
	3.80	....	6.00	....	....	....	Output for four hours ten minutes.
8	1.60						

Furthermore during the interval covering several days of freedom from physical and mental exertion the blood-pressure is not only lowered but it diminishes to such an extent that in some instances it reaches a normal level and in all of them at least approaches it. This fact is of distinct therapeutic importance. In the present series of observations it is very necessary to be informed concerning this marked variability before the effect of the sodium chloride is tested. It is obvious that with such an irregular base-line upon which to build experimental data that all results obtained must to a certain extent at least be interpreted by the observer who is, or ought to be, in the best possible position to render an unbiassed judgment as to what the effect of any given procedure on blood-pressure is and how far results may be influenced by the presence of spontaneous variations in the arterial tension due to the personal equation of the patient or unforeseen disturbances at the bedside. These much-needed control periods have usually been omitted in blood-pressure studies and thus many observations have lost their full value.

The control blood-pressure recorded as taken "just before test" is the final one of a series of readings. A number of observations were made in order that the minimal arterial tension pertaining at the time should be recorded and that the "spontaneous" variations in the blood-pressure occurring at the moment should be set aside. It is of interest to note that in more than half the cases this reading, taken under conditions that were carefully adjusted so as to insure

TABLE VI.—B. Y., MALE, AGED FIFTY-THREE YEARS. ESSENTIAL HYPERTENSION, SLIGHT DEGREE OF CARDIAC DECOMPENSATION ON ADMISSION, NO EDEMA, RENAL FUNCTION UNIMPAIRED. THE ONLY RISE IN BLOOD-PRESSURE NOTED AFTER GIVING 10 GM. OF SALT MAY BE ATTRIBUTED TO "WARD ROUNDS" AND "A VISITOR." ON REPEATING THE EXPERIMENT THERE WAS A SLIGHT RISE FOR A FEW MINUTES, WHICH MAY BE ATTRIBUTED TO THE NAUSEOUS DOSE ADMINISTERED, AND SUBSEQUENTLY THE BLOOD-PRESSURE DROPPED BELOW THE CONTROL LEVEL.

Date, 1921.	NaCl 24 hrs. urine, gm.	Diet.	Blood-pressure.			NaCl whole blood, mg. per 100 cc.	Remarks.
			Time.	Systolic.	Diastolic.		
Mar. 29	....	Mixed	5.00 P.M.	208	114	494	On admission to hospital.
Mar. 30 to May 5	12.30	Low-salt	....	190	110	....	Maximum for period.
	2.60	....	....	130	78	....	Minimum for period.
	7.36	....	....	....	....	....	Average for period (20 blood-pressure readings; 19 NaCl determinations).
May 5	6.00	Low-salt	11.04 A.M.	168	90		
			11.08	166	90		
			11.10	170	96		
			11.13	....	....	....	10 gm. NaCl in ½ glass of water taken by mouth.
			11.14	174	100		
			11.16	166	90		
			11.18	164	96		
			12.07 P.M.	154	88		
			12.09	162	84		
			12.16	152	82		
			1.14	162	90		
			1.17	150	80		
			1.20	164	88		
			1.30	....	....	544	
			2.08	192	110	....	Ward rounds.
			2.11	178	98		
			2.16	168	100		
			3.13	188	114	....	Visitor (wife).
			3.14	184	106		
			3.15	184	98		
			3.16	170	96		
			3.20	178	98		
			3.22	180	98		
			3.23	184	104	....	Visitor left.
			4.25	152	80		
			4.28	154	86		
			4.30	152	82	557	
			5.55	135	76		
			5.58	136	72		
			6.00	134	72		
			6.10	....	....	532	
			8.15	152	78		
			8.17	150	78		
			8.20	154	80		
May 11	7.10	Low-salt	10.38 A.M.	150	80		
			10.40	150	80		
			12.12	....	....	....	10 gm. NaCl in ½ glass of water taken by mouth.
			12.14	176	94		
			12.16	158	90		
			12.18	170	90		
			1.20	142	84		
			1.22	140	80		
			1.28	136	80		
			2.14	138	84		
			2.15	134	78		
			2.17	138	82		
			3.20	148	86		
			3.22	142	82		
			3.23	146	82		
			4.24	152	86		
			4.30	148	82		
			5.20	148	80		
			5.24	148	80		
			6.16	132	76		
			6.18	130	70		
			6.19	130	70		
May 12	7.00	Low-salt	....	162	90		
13	10.10	Low-salt					
14	8.60	Low-salt	....	162	96		
15	5.80	Low-salt					
16	3.30	Low-salt	....	160	88		
17	6.50	Low-salt					
18	5.80	Low-salt	....	154	94		
19	....	Low-salt	....	182	100	....	Discharged from hospital much improved.

TABLE VII.—J. H., MALE, AGED SIXTY-TWO YEARS. ESSENTIAL HYPERTENSION (RENAL FUNCTION UNIMPAIRED). MARKED "SPONTANEOUS VARIATIONS" IN BLOOD-PRESSURE, ESPECIALLY MARKED ON AUGUST 11 AND AUGUST 20 AT 3.35 P.M. SUBSEQUENT TO THE ADMINISTRATION OF 10 GM. OF NaCl THE BLOOD-PRESSURE DID NOT VARY IN ANY WAY FROM THE CONTROL PERIOD.

Date, 1920.	NaCl 24 hrs. urine, gm.	Diet.	Blood-pressure.			NaCl whole blood, mg. per 100 cc.	Remarks.
			Time.	Systolic.	Diastolic.		
July 29	....	"Salt-free"	....	200	100		
30	....	"Soft"	....	172	90		
31	....	"Soft"	1.45 P.M.	194	104		
Aug. 1	....	"Salt-free"					
2	7.62	"Salt-free"	10.20 A.M.	180	76	519	Blood NaCl before breakfast.
				176	92		
				188	100		
				160	96		
			8.40 P.M.	190	104		
3	8.80	"Regular"	1.40 P.M.	188	100		
4	5.29	"Regular"	10.20 A.M.	200	104	....	After exertion.
				188	98		
				182	98	....	After resting five minutes.
5	9.84	"Regular"	10.45 A.M.	194	98	....	After walking about ward.
				180	100	....	After resting.
6	8.56	"Salt-free"	11.30 A.M.	200	100	....	After conversing.
				162	90	....	After resting five minutes.
				158	96	....	After resting fifteen min.
				190	100	....	After walking.
7	....	"Salt-free"	10.15 A.M.	190	102	....	After conversing.
				170	98	....	After resting three minutes.
				164	98	....	After resting six minutes.
				168	98	....	After resting nine minutes.
9	2.81	"Salt-free"	9.00 A.M.	172	96	....	After walking about ward.
				160	96	....	After resting five minutes.
				178	96	....	After walking about ward.
				160	92	....	After resting.
				218	118	....	After conversing.
				204	106	....	After resting five minutes.
10	4.78	"Salt-free"	9.00 A.M.	218	110	....	After conversing.
				178	100	....	After resting five minutes.
11	3.24	"Salt-free"	11.00 A.M.	242	116	....	After relating an unpleasant incident.
				194	114	....	After resting five minutes.
12	4.61	"Salt-free"	2.00 P.M.	206	110	....	After conversing five min.
				180	100	....	After resting five minutes.
				220	110	....	After conversing three min.
13	2.32	"Salt-free"	1.30 P.M.	176	98	....	After resting.
				220	110	....	After conversing.
14	2.50	"Salt-free"	10.30 A.M.	164	92	....	After resting.
				180	96	....	After conversing.
15	2.80	"Salt-free"	9.00 P.M.	202	110	....	After conversing.
16	3.15	"Salt-free"	10.30 A.M.	200	100	....	After conversing.
				196	100	....	After resting three minutes.
				178	96	....	After resting six minutes.
17	1.70	"Salt-free"	10.00 A.M.	206	110	457	After conversing.
				178	98	....	After resting.
18	2.90	"Salt-free"	....	206	114	....	After conversing.
				190	110	....	After resting.
20	11.90	"Salt-free"	8.00 A.M.	....	....	443	
			8.15	....	....	....	Breakfast.
			9.10	210	104	....	After conversing.
				182	98	....	After resting three minutes.
			9.15	....	....	....	10 gm. NaCl by mouth in 150 cc H_2O.
			10.05	210	112	....	After conversing.
				190	100	....	After resting three minutes.
				190	100	....	After resting six minutes.
			10.20	....	....	527	
			11.00	170	90	....	Resting.
				172	90	....	Resting.
			12.00 M.	222	114	....	After conversing.
				202	104	....	After resting five minutes.
			12.20 P.M.	....	....	520	
			1.20	200	104	....	After resting.
				184	100	....	After resting.
				210	110	....	After conversing.
			2.45	....	....	494	
			3.35	242	120	....	After death of patient in next bed.
				210	110	....	After resting five minutes.
				210	112	....	After resting ten minutes.
			4.30	228	114	....	After conversing.
				214	110	....	After resting five minutes.
			5.45	186	106	482	
21	....	"Salt-free"	10.00 A.M.	182	108	....	After conversing.
				180	100	....	After resting five minutes.

TABLE VIII.—M. D., FEMALE, AGED FIFTY-SIX YEARS. ESSENTIAL HYPERTENSION, SLIGHT DEGREE OF INSUFFICIENCY (WASSERMANN REACTION NEGATIVE, NO SIGNS OF LUES), NO SIGNS OF MYOCARDIAL INSUFFICIENCY, NO IMPAIRMENT OF RENAL FUNCTION (URINARY SPECIFIC GRAVITY VARIED BETWEEN 1.016 AND 1.030). BLOOD ANALYSES AS MG. PER 100 CC: UREA, N 21.4; URIC ACID, 2.8; AND CREATININE, 2.2. VARIOUS EXPERIMENTS AND CONTROL PERIODS. IN NONE OF THE EXPERIMENTS DOES 10 GM. OF SODIUM CHLORIDE PRODUCE A DEFINITE RISE OF BLOOD-PRESSURE.

Date, 1921.	NaCl 24 hrs. urine, gm.	Diet.	Blood-pressure.			NaCl whole blood, mg. per 100 cc.	Remarks.
			Time.	Systolic.	Diastolic.		
April 6	....	Low-salt	8.00 P.M.	224	120	494	On admission to hospital.
April 7–14	7.83	"Salt-free"	....	232	130	....	Maximum for period.
	1.52		....	180	100	....	Minimum for period.
	3.91		....	....	....	....	Average for period.
14	3.20	"Salt-free"	11.30 A.M.	....	....	....	30 cc of qitter, pink-colored water taken by mouth.*
			12.07 P.M.	190	108		
			12.10	186	106		
			12.12	190	108		
			1.19	176	108		
			1.21	180	110		
			1.22	170	104		
			1.25	184	104		
			4.11	178	109		
			5.17	180	104		
			5.19	178	104		
15	2.24	"Salt-free"	11.50 A.M.	176	108		
			11.56	176	110		
			3.00 P.M.	....	....	....	Small stomach tube introduced; patient somewhat disturbed.
			3.35	190	110		
			3.37	180	110		
			3.40	186	110		
			3.41	180	110		
			3.45	....	....	....	50 cc of colored water introduced through tube.*
			3.47	194	110		
			3.50	200	114	....	Tube removed.
			8.39	166	104		
			8.42	166	104		
16	2.18	"Salt-free"	3.15 P.M.	192	116	....	Maximum.
			1.39	166	92	....	Minimum (6 readings).
17	3.66	"Salt-free"	12.06 P.M.	184	110		
			12.09	180	110		
			12.11	184	110		
			2.15	....	....	....	Tube introduced.
			2.25	197	116		
			2.26	....	....	....	10 gm. NaCl in 50 cc colored water given through tube;* nauseated; drank 1 glass of water; no vomiting; tube removed.
			2.27	202	116		
			2.57	197	118	....	Visitors after 3 P.M.
			4.13	194	118		
			4.15	185	114		
			4.16	188	114		
			5.42	198	114		
			5.43	192	114		
			5.45	184	114		
			5.47	192	114		
			7.18	200	120		
			7.20	192	116		
			7.23	196	116		
			7.24	188	114		
			8.54	192	106		
			8.57	188	106		
			9.00	180	106		
			9.02	186	108		

Date, 1921.	NaCl 24 hrs. urine, gm.	Diet.	Blood-pressure.			NaCl whole blood, mg. per 100 cc.	Remarks.
			Time.	Systolic.	Diastolic.		
18	8.00	"Salt-free"	12.23 P.M.	196	118	....	Maximum.
			4.06	182	106	....	Minimum (4 readings).
19	5.30	"Salt-free"	3.00 P.M.	202	134	....	3 visitors (1 reading).
20	3.73	"Salt-free"	10.33 A.M.	166	94	....	
			10.35	176	104	....	After conversing.
			10.38	164	100	....	
			1.45 P.M.	....	....	....	Tube introduced.
			1.50	180	106		
			1.53	174	108		
			1.54	174	108	513	
			2.38	....	....	....	10 gm. NaCl in 50 cc colored water given through tube;* tube removed.
			2.41	204	114		
			2.48	190	110		
			3.35	192	104	563	
			3.36	182	110		
			3.38	178	104		
			3.41	178	100		
			6.59	184	106	544	
			7.02	182	110		
			7.03	178	110		
			7.07	180	114		
			9.23	178	114		
			9.25	179	112	525	
21	7.60	"Salt-free"	12.25 P.M.	182	118	....	Maximum.
			4.06	176	114	....	Minimum (5 readings).
22	6.90	"Salt-free"	7.55 P.M.	182	114	....	Maximum.
			7.58	176	106	....	Minimum (4 readings).
23	4.20	"Salt-free"	3.00 P.M.	170	103	....	Maximum.
			10.11 A.M.	158	98	....	Minimum (5 readings).
25	1.50	"Salt-free"	12.15 P.M.	180	112	....	Maximum.
			9.03	166	108	....	Minimum (4 readings).
April 26 to May 5	4.50	"Salt-free"	....	194	120	....	Maximum for period.
	1.20	....	....	150	100	....	Minimum for period (33 readings).
	3.45	"Salt-free"	....	....	....	....	Average for period.
May 5	....	"Salt-free"	1.01	164	114		
			1.02	164	116		
			1.04	164	112		
			1.50	....	....	....	Tube introduced.
			2.45	....	....	....	10 gm. NaCl in 50 cc colored water given through tube; tube removed.
			2.50	167	112		
			2.54	165	112		
			2.58	160	110		
			3.45	162	116		
			3.48	162	116		
			3.49	156	116		
			3.50	156	116		
			3.52	161	120		
			5.04	182	116	....	Patient standing.
			5.08	170	114		
			5.10	178	120		
			5.12	172	124		
			5.13	174	120		
			5.15	173	126		
			8.30	168	126		
			8.31	164	128		
			8.32	168	126		
May 6	....	"Salt-free"	6.55 P.M.	166	106		
			6.57	166	106		
7	....	"Salt-free"	2.40 P.M.	170	110		
9	....	"Salt-free"	8.00 P.M.	176	100		
				182	110		
10	....	"Salt-free"	12.00 P.M.	196	120	....	Patient sitting out on porch.
			12.17	194	120		
11	....	"Salt-free"	11.10 A.M.	196	124		

* Bitter substance used was a few drops of tincture of myrrh; coloring matter was a few drops of phenolsulphonephthalein.

TABLE IX.—J. T., MALE, AGED FIFTY-SIX YEARS. ESSENTIAL HYPERTENSION RECOVERING FROM MYOCARDIAL INSUFFICIENCY. NO IMPAIRMENT OF RENAL FUNCTION. THE BLOOD-PRESSURE DOES NOT RISE MORE THAN COULD BE ACCOUNTED FOR BY "SPONTANEOUS VARIATIONS" AFTER TAKING 10 GM. OF SALT IN CAPSULES.

Date, 1920.	Diet.	Blood-pressure.			NaCl whole blood, mg. per 100 cc.	Remarks.
		Time.	Systolic.	Diastolic.		
July 11-	"Salt-free"	....	238	130	485	Maximum for period.
29	....	....	190	100	478	Minimum for period (19 blood-pressure readings and 2 blood NaCl determinations).
29	"Salt-free"	9.45 A.M.	196	110	488	
		10.00	....	....	....	10 gm. NaCl in 5 capsules by mouth with 180 cc of water.
		10.10	194	102		
		10.40	....	....	....	Vomited small amount.
		11.10	208	112		
		11.15	....	....	506	
		11.30	....	....	....	Drank 90 cc of water.
		12.10 P.M.	206	98		
		1.10	192	92		
		2.15	198	102		
		2.20	....	....	513	
		4.05	198	104		
		7.45	208	110		
		8.00	....	....	513	
		9.45	188	104		
30	....	1.30 P.M.	192	100		

TABLE X.—A SUMMARY OF THE DATA CONTAINED IN TABLES IV, V, VI, VII, VIII AND IX. THE VARIABILITY OF THE BLOOD-PRESSURE DURING THE CONTROL PERIOD IS SHOWN. THERE IS NO RISE IN BLOOD-PRESSURE THAT MAY BE ATTRIBUTED TO THE DIRECT EFFECT OF GIVING SODIUM CHLORIDE IN 10 GM. DOSES.

Observation.	Case.	Substance given in test.	Control blood-pressure.*			Maximal blood-pressure* after test-substance.			Minimal blood-pressure after test-substance.	
			Several days before test.		Just before test.	Maximal* blood-pressure.	Minutes after test-substance.	Possible cause for maximal blood-pressure.	Within 2 hrs.	2 to 4 hrs.
			Maximal.	Minimal.						
1 . .	E. T.	Colored water	238/120	160/90	184/104	214/106	150	Headache, malaise	188/96	190/100
2 . .	A. K.	NaCl, 7 gm.	220/98	172/74	196/96	266/126	13	Nausea	214/98	189/92
3 . .	B. Y.	NaCl, 10 gm.	190/110	130/78	170/96	192/110	175	Ward rounds	152/82	150/80
4 . .		NaCl, 10 gm.	192/110	134/72	150/80	176/94	2	Nausea	136/80	134/78
5 . .	J. H.	NaCl, 10 gm.	242/116	158/96	182/98	242/120	380	Patient died in next bed	170/90	202/104
6 . .	M. D.	NaCl, 10 gm.	232/130	170/104	197/116	202/116	1	Nausea	185/114	184/114
7 . .		NaCl, 10 gm.	202/134	180/106	174/108	204/114	3	Nausea	178/100	
8 . .		NaCl, 10 gm.	204/114	150/100	164/112	182/116	139	?	156/116	161/120
9 . .	J. T.	NaCl, 10 gm.	238/130	190/100	196/110	208/112	70	Vomited	194/102	192/92

* The double figure under each observation indicates the systolic and the diastolic blood-pressure.

the greatest possible degree of mental and physical relaxation, not only at the time but also for a number of preceding days, was considerably higher than the lowest previous observations. This serves to show how uncontrollable a factor the height of arterial tension really is. However, with the control period covering several days and a careful adjustment of conditions immediately before the administration of the sodium chloride, it was felt that as accurate a base-line as possible had been established and the actual experimental periods were instituted.

In none of these patients except one did the salt produce any untoward symptoms; in this instance they were alarming. This point has already been discussed and the conclusion previously arrived at may be repeated here: Sodium chloride may be administered in large doses to cases of essential hypertension provided no sequelæ of the increased blood-pressure are present; if renal, cardiac, cerebral or possibly other complications are present it is not safe to give salt in large quantities. Failure to differentiate between "pure" essential hypertension and the form of the disease in which there is secondary involvement of various important organs has led some authors to conclude erroneously that sodium chloride produced dangerous manifestations in all cases. The patient exhibiting these untoward symptoms is not included in the present series.

If salt effects a rise in blood-pressure this should occur within two hours after the administration of the sodium chloride, because it is within this period that blood chlorides attain their maximum level (Tables VII and VIII); therefore the delayed sudden rise in blood-pressure occurring after 120 minutes in observation 5, Table X, may be discounted. The isolated rise coming on immediately after the dose of salt is in all probability due to the attending nausea observations 2 and 7, Table X. This leaves virtually no distinct rise in blood-pressure that can not be accounted for by other agencies than the postabsorptive effect of the salt. A rise of 30 points in the blood-pressure may be considered as a reasonable increase during the experimental period that may be attributed to spontaneous variations in arterial tension during a period of two to four hours. Observation 1, the control experiment in which colored water was administered instead of salt solution, showed a rise of 30 mm. of mercury, substantiating the above supposition. If the problem is studied from this angle and any rise of arterial tension of 30 or less is regarded as being within the probable unavoidable variation taking place during the period of the experiment, it may be noted that the maximal rise of the systolic blood-pressure was (as given in Table X).

5	mm.	of	mercury	in	observation	6
12	"	"	"	"	"	9
18	"	"	"	"	"	8
22	"	"	"	"	"	3
26	"	"	"	"	"	4
30	"	"	"	"	"	7

This leaves only observations 2 and 5 with a distinct rise in blood-pressure (that is one higher than 30 mm. of mercury) that might be considered as indicating any possible effect of the sodium chloride.

There is another point of view from which the present observations may be analyzed. If salt causes a rise in blood-pressure the arterial tension should not drop while the sodium chloride is exerting its effect. Therefore the study of the minimal blood-pressures obtained would be of as great, if not greater importance, than the maximal. As has already been noted it is within the first two hours after ingestion that the salt is absorbed from the intestine. Neither in the first two or the second two hour period after taking sodium chloride does the minimal blood-pressure rise appreciably above the control reading taken at the time the experiment was started; in most instances the minimal blood-pressure is distinctly lower. Therefore from this point of view, as well as from those previously stated, the ingestion of 10 gm. of sodium chloride does not appear to increase arterial tension.

The observations given in detail in Tables IV to IX have been analyzed from other angles and have not been found to yield any indication that the doses of salt administered were productive of an increased blood-pressure. The difficulties attending the conduction of these experiments, especially in regard to obtaining a proper value for the "spontaneous" variations in blood-pressure, have been studied with some care and it is believed that they have been eliminated as far as this can be done.

Conclusions. Marked "spontaneous" variations occur in the blood-pressure of all individuals. In cases of hypertension a very great diminution of arterial pressure usually occurs during periods of mental and physical relaxation. This variability in blood-pressure has not been accorded sufficient attention when the effect of diet, drugs, etc., upon arterial tension has been studied.

The protein foods do not increase blood-pressure.

The starchy foods may increase blood-pressure indirectly by bringing about obesity.

There is no definite evidence in the literature that sodium chloride raises blood-pressure. The level of the blood chlorides bears no relation to blood-pressure. In a series of experimental observations the ingestion of 10 gm. of salt failed to raise the blood-pressure in cases of hypertension.

DIABETES INSIPIDUS: A CASE REPORT FOLLOWING EPIDEMIC ENCEPHALITIS WITH ENORMOUS POLYURIA.*

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The patient, J. I., aged sixteen years, a laborer in a packing house, was admitted to the Cook County Hospital, December 16, 1919, complaining of diplopia, marked drowsiness, pain in the back of the neck and night sweats, for one week previous to admission.

Previous Illness. He had chorea at the age of ten years; measles, scarlet fever and whooping-cough in childhood. He gave no history of any venereal infection.

Family History. Negative.

Examination. Examination revealed a slight bilateral ptosis. The pupils reacted to light rather sluggishly. There was a paresis of the left side of the face involving both the upper and lower group of muscles. The spinal fluid was normal. The Wassermann tests upon the blood and spinal fluid were both negative. Urine was normal. Leukocyte count was 15,200.

Diagnosis. Diagnosis was epidemic encephalitis.

The patient made a prompt recovery within three weeks and returned home and to his work. During his stay in the hospital a twenty-four-hour sample of urine measured 3000 cc.

He was admitted a second time to the Cook County Hospital on the service of Dr. J. A. Capps, September 7, 1921, approximately two years later. The complaints on entrance were great thirst, dry mouth, ravenous appetite and frequent micturition.

He said that he had been complaining of this extreme thirst during the past year and that he was compelled to pass urine almost every hour of the twenty-four. This became so annoying that he could not hold a position.

Examination of the eyes, nose and throat was negative. The optic disks were normal. He had one infected tooth. The thyroid gland was negative. Heart, skin and gastrointestinal tract were negative. Muscles, bones, joints and glands were normal. The liver and spleen were not palpable. The blood-pressure was 102 systolic and 80 diastolic.

Examination of the nervous system showed the deep reflexes to be normal and no sensory disturbances or evidences of paralyses were present. Roentgen rays of the sella turcica showed it to be normal in size and contour.

* Read before the Chicago Society of Internal Medicine, April 24, 1922.

TABLE I.

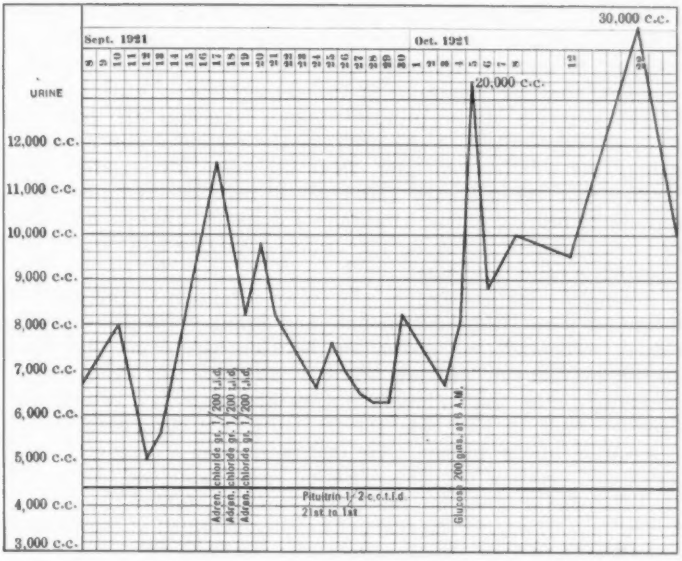
Date, 1921.	Intake in cc.	Output in cc.	Remarks.
Sept. 8	5,730	6,750	
" 9	5,400	no record	Urea N. 13.5 mg.; uric acid, 2; creatinin, 1.51; sugar, 95; chlorides 620 (by Dr. J. Kendall).
" 10	5,710	8,000	
" 11	6,810	6,240	
" 12	5,160	5,000	
" 13	7,080	5,500	Adrenalin chloride gr. $\frac{2}{100}$ t. i. d. in sterile oil.
" 15	2,970	18,800	Mosenthal diet.
" 17	8,200	11,500	Adrenalin as on September 13.
" 18	7,500	9,600	Adrenalin as on September 13.
" 19	8,880	8,160	Adrenalin as on September 13.
" 20	7,500	9,600	Adrenalin as on September 13.
" 21	8,880	8,160	Urea N., 9.34; uric acid, 1.95; creatinin, 1.43; sugar, 83; chlorides, 545.
" 24	7,590	6,500	Pituitrin $\frac{1}{2}$ cc t. i. d., until September 30*. Blood pressure 138–96, twenty minutes after pituitrin.
" 25	8,100	7,500	Relief from extreme thirst.
" 26	8,400	7,000	
" 27	5,940	6,500	
" 28	7,860	6,240	
" 29	7,850	6,240	
" 30	9,900	8,160	
Oct. 2	8,820	7,200	
" 3	6,750	6,720	
" 4	.....	.....	200 gm. glucose given.
" 5	15,660	20,000	
" 6	11,070	8,640	Basal metabolism,—8.5.
" 7	9,960	9,680	
" 14	.....	27,000	
" 20	.....	30,000	
" 23	.....	.....	Again given pituitrin as before.
" 27	.....	16,000	
Nov. 2	.....	13,000	

* Following pituitrin, the patient complained of a sensation as though electricity was passing through his body, and of headache and dizziness.

Following the administration of 200 gm. of glucose on October 7, sugar was not detected in the urine after three, six and twenty-four hours. The blood chemistry before the administration of glucose showed 100 mg. of sugar. One hour following the administration of glucose it showed 90.9; after two hours, 66.7 mg.; after three hours, 117.01; after four hours, 55.5 mg.

October 10, 1921, the phenolphthalein test showed 75 per cent elimination during the first two hours. Cystoscopic examination made previously by Dr. Culver revealed a normal mucosa. Phenolphthalein tests were carried out as follows: the right kidney showed the presence of phenolphthalein within three minutes following the injection intravenously. Two ounces of urine were obtained within thirty minutes and showed an excretion of 9 per cent (normal is 25 to 30 per cent). The left kidney showed the appearance of solution in three minutes following injection and 12 per cent excretion within thirty minutes. On this day, 200 gm. of glucose were again given and no sugar appeared in the urine, showing an increased sugar tolerance.

Because of certain peculiar mental manifestations, he was transferred to the Psychopathic Hospital on October 10, 1921. The social service report at that time stated that the patient reached the seventh grade in public school, that he had worked rather steadily as a packer in the stockyards. There was no history of delusions or hallucinations reported. The Binet-Stanford examination, made by Dr. S. H. Tulchin, showed a chronological age of eighteen years, a mental age of eleven years and five months, and an intelligence quotient of 71.3, classifying him as a borderline case mentally. Further mental examination showed orientation as to time, place and person to be good. Memory past and present was good. Retention was good, general information poor,



judgment poor and reaction to environment good. Emotional attitude adequate. As to behavior, he was quite coöperative, answered questions promptly, coherently and to the point. No paranoiac trends were elicited. Further investigation showed that the patient had been arrested eight months previous to entering the hospital for making advances to a girl living next door to him, and two weeks later he again exposed himself to the same girl, because he thought she had smiled at him.

Diagnosis. Organic brain disease with a judgment defect, following epidemic encephalitis.

In reference to the extent of the polyuria in diabetes insipidus, Edwards[1] says that it runs from 10 to 40 and even 90 pints per

day; Jeanselme and Weil[2] say from 10 to 20 liters per day. In cases reported by Gibson and Martin[3] and Fracassi,[50] the amount of urine reached 15 liters per day; Nasso[5] reported 15 liters; v. Hoesslin,[42] 20 to 24 liters; Herrick,[6] 10 liters; while Trousseau[7] reported an early case in which the urine reached the enormous quantity of 43 liters in twenty-four hours. It will thus be seen that in this case the urinary output in twenty-four hours is one of the largest recorded in the literature.

It is only within the present decade that the morbid entity known as diabetes insipidus or, as it was previously styled, essential polyuria, was definitely removed from the classification of urological diseases, and its pathogenesis referred to some lesion of the nervous mechanism governing the kidney functioning and elimination. However, exact appreciation of the nervous mechanical disturbance is a matter concerning which there is even at the present time no universal agreement, although it is generally conceded that the syndrome of the disease follows a disturbance of the secretion of the pituitary gland, especially the posterior lobe, or some injury to the brain in the region of the pituitary gland. As will be seen later, there are some investigators who believe that the pituitary gland *per se* may be exempted from any direct bearing on the causation of diabetes insipidus and that the brain centers governing the urinary secretion and output are situated outside this gland.

Among the earliest writers who called attention to this morbid condition were Willis,[8] Simmonds[9] and Frank.[10] Willis, in 1682, clearly recognized the distinction between saccharine and non-saccharine diabetes without, however, ascribing any exact cause; Simmonds, more than a hundred years later, described two clinical cases. Frank, in 1792, was the first to give a clear pathological description of the disease. He described it as a long-continued increased secretion of non-saccharine urine, and was convinced that the condition was not due to any diseased state of the kidney. Frank's description is classical and may be accepted at the present day, if we add to it intense polydipsia.

Since that time, the immense literature which has grown up around this subject may be described either as clinical reports, supporting favorite theories regarding the uncertainty of the origin of the condition, or experimental investigations, with a view of discovering the factors concerned with its appearance. It was known that the polyuria was accompanied by polydipsia, but it was not conceded that the former was dependent upon the latter; it was known that the concentration of salts in the urine was disturbed, and different metabolic theories were enunciated to account for it; the blood supply to the kidney and the nervous control of the organ were incriminated and, by degrees, led to a

recognition of the higher centers, disturbance of which was responsible for the development of the syndrome.

The disease is uncommon. In the Zurich Medical Clinic, in nearly 36,000 patients observed by Eichhorst during 1876 and following years, he saw only 17 with diabetes insipidus; in the Charité Hospital, Berlin, from 1877 to 1896, Gerhardt observed 55 cases in 113,600 patients. Futcher[20] says that 7 cases of diabetes insipidus were found in over 400,000 patients treated at the Johns Hopkins Hospital, from 1889 to 1904. The disease, therefore, is observed in less than one-tenth of 1 per cent of all cases of disease. It is seen more frequently before the fortieth year of life, and women are affected more than men. Janzen and Brockmann[11] state that it has been observed as a familial disease, and mention 7 instances where the members of families showed a tendency toward or actual development of diabetes insipidus.

In the older views, diabetes insipidus was considered to be of two types: (1) Primary or idiopathic without any evidence of organic lesion, and (2) symptomatic with evidence of organic disease, such lesion being considered as the primary cause. The pathogenic factors concerned are differently estimated as: (1) Primary polydipsia, due to some nervous disturbance; (2) due to pathological condition of the kidneys; (3) due to nervous or vascular disturbance of the kidney function, not, however, dependent upon an organic brain lesion; (4) organic disease of the hypophysis cerebri, especially of its posterior lobe; (5) organic lesion of the centers governing urinary secretion and kidney action—such centers not necessarily being situated in the hypophysis.

The view that diabetes insipidus of idiopathic type exists is scarcely held today; nor is it considered that the polyuria is secondary to a primary polydipsia, which view was supplanted by Ebstein[12] and others. The kidney origin of diabetes insipidus was brought into prominence in 1905 by Meyer,[13] who came to the conclusion that the idiopathic type was primarily a renal polyuria, due to a functional failure of the kidneys which rendered them incapable of secreting concentrated urine, *i. e.*, urine above a certain low specific gravity. Histological examination of the kidneys in cases of diabetes insipidus did not, however, support the view that the condition is due to structural alterations. Further contributions of note concerning diabetes insipidus as being due to a pathological condition of the kidneys were made by Tallqvist,[14] Socin,[15] Forschbach and Weber[16] as well as others.

In 1909, Engel[17] enunciated the view that a prolonged nervous stimulus, possibly in the medulla, excited the glomeruli to greater secretive activity, or the tubules to diminished resorption, or both. Fitz[18] recently discussed the nervous control of the kidney and of its vascular supply. He points out that the researches of Claude Bernard and others have shown that section of the cord at

the sixth or seventh cervical vertebra produced an immediate suppression of urine and that section below the twelfth dorsal had practically no effect upon the secretion. In the intermediate sections, the results, as regards the urinary secretion were variable. The studies of Schaefer and Herring[19] have shown that pituitary secretion has a specific dilating effect upon the renal vessels. Fitz thinks that the nerve fibers governing the kidney pass from the medulla to the level of the sixth or seventh cervical vertebra, where they leave the cord, and that an experimentally produced polyuria is an irritative phenomenon or that a brain lesion (even without focal symptoms) may cause hypersensitiveness of the renal vessels either by stimulation of the vasomotor nerves of the kidney or through hypersecretion of the hypophysis. In either case, a polyuria might result from hyperirritability of the renal vessels.

Diabetes insipidus is more usually observed when there is some manifest or implied brain lesion present. The lesion from its symptomatology is usually conceded to be in the hypophysial or closely adjoining region. But, on the other hand, diabetes insipidus may be observed without any clinical showings which would suggest a brain lesion.

The Presence of a Hypophysial Hormone. Bauer and Aschner[21] have very recently expressed the view that diabetes insipidus may find its origin in the kidney or its innervation, dependent upon some disturbance in the nerve centers in the brain. Stimulation of the superior cervical sympathetic ganglion, and a consequential effect upon the brain centers governing the mechanism of metabolism, was enunciated as a hypothesis by Weed and Jacobsen,[22] in 1913. Maranon[23] thinks that the posterior lobe of the pituitary physiologically exercises a controlling action upon the elimination of water through the renal filter and thus produces polyuria through any disturbance. The hypophysial hormone may act partly directly upon the kidney cell or partly by the means of the nervous system. Maranon thinks it probable, as both Cushing and Biedl have suggested, that the hypophysial hormone ascends by the *tuber cinereum* and acts upon the proximal mesencephalic centers.

Bailey and Bremer[24] recently have, as a result of experimentation come to a different conclusion which will be dealt with presently.

Although the brilliant experimental work of Crowe, Cushing and Homans[25] in 1910, had shown that in animals an experimental partial hypophysectomy was followed by polyuria among other effects, yet it cannot be said that a definite connection between the hypophysis cerebri and the syndrome of diabetes insipidus was completely accepted until the findings of Farini,[26] who first, in 1913, showed that injections of hypophysial extract modified polyuria. This finding was confirmed by Rosenbloom,[27] Maranon,[23]

Motzfeldt,[28] Lereboullet[29] and many others since that time. Although the modification is transitory, the effect appears to be absolutely specific for pituitary gland extract, and polyuria recurs as soon as the injections are discontinued or shortly after.

As early as 1901, Magnus and Schaefer[30] had shown that pituitary extract caused an increased urinary secretion and output. Schaefer and Herring[19] showed later that the urinary effects of hypophysial extracts were due alone to derivatives from the pars intermedia and they claimed that the diuretic action was the result of a property of this secretion directly stimulating kidney cell action as well as locally dilating the kidney vessels. They thought that diabetes insipidus might be a manifestation of a superactive hypophysis.

Pars Intermedia. In 1913, Lewis and Matthews,[31] experimenting with dogs, came to the conclusion that the clinical and experimental data showed diabetes insipidus to be due to hypersecretion of the pars intermedia. But Roemer[32] showed that some cases of diabetes insipidus might be due to lack of secretion of the pars intermedia and not to hyperfunction.

Posterior Lobe Secretion. Motzfeldt's important contribution,[29] in 1918, concerning 3 cases of diabetes insipidus, in which all the symptomatology pointed to an insufficiency of posterior lobe secretion of the pituitary, has been generally accepted as showing this to be the part most involved in the syndrome of diabetes insipidus.

The more recent investigations of Leschke, Houssay, Camus and Roussy and Bailey and Bremer have, however, rather tended to focus the cause of diabetes insipidus upon some injury to the brain centers governing urinary secretion other than to the hypophysis.

Tuber Cinereum and the Hypothalamus. Leschke,[33] in 1917, showed that diabetes is not of hypophysial origin because total extirpation of the gland has no influence upon the secretion of urine, when sufficient care is exercised that the *tuber cinereum* and no other part of the brain be touched. When the pituitary gland alone, and without injury to other parts, is removed polyuria is never observed; but, on the other hand, piqûre in the *tuber cinereum* produces polyuria. Leschke thinks it most probable that the brain center for the secretion of urine is situated here near the centers for metabolism and of the sympathetic nerves of the eye, and that very probably diabetes insipidus is produced by a disturbance of this center. The hypophysis has no relation to it and it is only when a hypophysial tumor presses upon the center, or some other such condition, that polyuria arises. Besides, it is known that polyuria may occur in basal meningitis and other pathological conditions, where there is a normal pituitary gland.

Camus and Roussy,[34] in 1913, showed by animal experiments that by puncturing the hypothalamus they were able to produce

polyuria. These authors later showed[34] that after removal of the hypophysis of dogs, the administration of pituitary extract did not improve the syndrome of diabetes insipidus, and they, hence, concluded that the essential factor in this disease might be a lesion of some adjacent region in the brain. Camus and Roussy were satisfied from their experimental work upon dogs that it was not the removal of the pituitary gland that determined polyuria but a lesion of the base of the brain corresponding to the optopeduncular space.

Houssay,[35] from experiments reported in 1915–1916, established a cerebral base zone, an injury to which produced polyuria. This zone is bounded in front by the optic chiasm and posteriorly by the peduncle protuberance. The posterior lobe of the pituitary body may constitute a part of this zone, but Houssay does not think it probable.

Bailey and Bremer,[24] quite recently experimenting upon dogs and using the lateral route of approach to the hypophysis devised by Paulesco and Cushing which avoids the probability of injuring it, have found that polydipsia and polyuria are produced with certainty if even a very slight injury to the postinfundibular region of the hypothalamus occurs. The polyuria thus produced may be transitory or permanent. The experimental diabetes insipidus produced does not depend upon a disturbance of a supposed nervous or vascular regulation of the kidney, as it can be induced in animals whose kidneys have been denervated. Lesion of the tuber cinereum has also produced persistent polyuria with adiposogenital dystrophy in dogs. Lesion of the base of the brain outside of the para-infundibular region does not produce polyuria, according to these authors. There is no evidence of any hormone regulating the kidney, especially a pituitary hormone.

It is evident from these findings of Camus and Roussy, Leschke, Houssay and Bailey and Bremer that there is very great divergence of opinion at the present time with regard to the exact location in the brain, injury to which sets up polyuria; general opinion may be taken as in accordance with the editorial view expressed in the *Journal of the American Medical Association*[36] that, in the present conflicting state of evidence, it cannot be accepted that a disorder of the pituitary body is in all cases the cause of polyuria.

Polyuria, seemingly, is a nervous phenomenon, which may be caused by any irritation or lesion of the optopeduncular region; or of the postinfundibular region of the hypothalamus; and in the front rank of such lesions is the pressure produced by enlargement or tumor of the hypophysis. Clinically, although polyuria is modified by hypophysial extract injections, it has never been definitely proved that a lesion of the hypophysis itself is the only cause of diabetes insipidus.

In support of these views are the cases reported by Veil,[37] in which polyuria and increase of chlorides in the urine were caused by piqûre in the floor of the fourth ventricle; when the puncture was made in the midbrain there was polyuria with decreased chlorides. Veil, in fact, called attention to two types of diabetes insipidus, in one of which the chlorine content of the blood is increased and in the other diminished.

Goldzieher,[38] Berblinger[39] and Simmonds[40] have all referred to the relation between diabetes insipidus and lesions in and about the pituitary, especially in its posterior part; the view of Newmark[41] is that polyuria may or may not follow neurohypophysial disease, and that the neurohypophysis is not the only region, disease of which is followed by polyuria and polydipsia. The medulla oblongata figures occasionally in the pathology of diabetes insipidus and v. Hoesslin[42] and Gierke[43] reported cases of diabetes insipidus with tumor or atrophy of the pineal gland. In Gierke's case there was, however, concurrent disease of the third ventricle and of the neurohypophysis as well. Bailey and Bremer, as we have seen, limit diabetes insipidus symptoms to injury of the post-infundibular region.

Despite the experimental demonstrations of Læschke, Houssay, Camus and Roussy and Bailey and Bremer, the fact remains that hypophysial extract injection seems to be specific in the treatment of diabetes insipidus; and, moreover, in many clinical cases of diabetes insipidus, an actual lesion of the pituitary body can be demonstrated. Cushing[44] showed that simple operative manipulation of the posterior lobe led to profuse diuresis and that its ablation caused transitory polyuria. Chiasserini's[45] dog experiments showed that hyperplastic lesions of pars intermedia sometimes induced intense polyuria; bacilli introduced into the sella turcica caused progressive changes in the anterior portion of the gland accompanied by intense polyuria. In Neuberger's case[46] there was destruction of the pars nervosa by a cancerous metastasis; in Maranon and Pinto's case[47] a bullet lodged in the base of the hypophysial stalk; in Luzzato's case,[48] hemorrhage into the stalk; in Catterina's case,[49] a probable compression of the hypophysis relieved by trepanation and disappearance of the symptoms. As previously stated, Crowe, Cushing and Homans[25] reported that a polyuria, either transitory or prolonged, frequently accompanies hypophysectomy. In Franke's case,[51] a bullet was lodged at the base of the pituitary.

The exact etiological factors concerned in diabetes insipidus, if it is to be considered as an independent syndrome, must remain unsettled until more definite knowledge is obtained regarding the precise location of the brain centers governing the action of the kidney, and what conditions affect such centers.

Syphilis as an Etiological Factor. Owing to the frequency with which it invades the brain, syphilis is generally admitted as an important etiological factor, and cases have been reported by Fracassi,[50] Cammidge,[52] Dameno,[53] Chiari[54] among others. In Fracassi's case the patient was passing 15 liters of urine per day, and the polyuria quickly subsided under specific treatment. Chiari's case was very similar. Cammidge thinks that his case was the result of parasyphilitic changes at the base of the brain, which interfered with the passage of the secretion of the hypophysis into the cerebrospinal fluid. The sudden change of pressure under lumbar puncture broke down adhesions and opened a passage again for the secretions. In Dameno's case there was apparently a syphilitic process which had induced diffuse infiltration involving the optic chiasm and pituitary body.

In syphilitic cases the type is either that of a gumma in the floor of the fourth ventricle, in the pituitary or in the brain region outlined by Houssay, which has been previously referred to, or else the syphilitic process may set up a basal meningitis or an endarteritis with connective-tissue proliferation.

Globus and Strauss[58] report a case of teratoid cyst of the hypophysis in a girl, aged six years, who developed polydipsia and polyuria. The tumor was adherent to the optic chiasm and, extending posteriorly, filled up the entire interpeduncular space. The *tuber cinereum* and mammillary bodies could not be identified, the third ventricle was almost obliterated. The hypophysis was small in size and compressed while the infundibular portion of the hypophysis showed no change except compression. They are inclined to think the autopsy findings in this case support the experimental work of Bailey and Bremer.

No Hormone in the Spinal Fluid. It has been considered that the cerebrospinal fluid has some effect upon the inhibitory action of pituitary extract upon the polyuria of diabetes insipidus; or, at least, that the extract was only effective after its discharge into the cerebrospinal fluid. Maranon and Gutierrez's[55] experimental research upon this point is rather convincing. These authors found that by injecting healthy rabbits with cerebrospinal fluid from a normal healthy human subject there was an increase of diuresis. But, if instead of injecting spinal fluid, extract of the posterior or middle lobe of the hypophysis was injected there was considerable diminution in the quantity of urine eliminated in twenty-four hours. If instead of obtaining the injected cerebrospinal fluid from a normal man, it was obtained from a patient with diabetes insipidus the effects on rabbits were the same as in the case of fluid obtained from a normal subject.

The intraspinal injection of pituitrin diluted with patient's own spinal fluid (*i. e.*, 0.5 cc of pituitrin diluted in 2 cc of spinal fluid of the patient injected intraspinally), caused only the same amount

of reduction as a subcutaneous injection of the same quantity of pituitrin. This was verified in different experiments.

The general results showed that there was no diffusion of an oliguric hormone in the spinal fluid.

The Effects of Lumbar Puncture. But the spinal fluid can act upon the polyuria by its tension. In the case reported by Herrick,[56] withdrawal of only 5 cc. by lumbar puncture caused an almost immediate gradual reduction of the polyuria from more than 11,000 cc. per day to little over 600 cc. In Graham's traumatic case,[57] lumbar puncture likewise caused an immediate reduction of a polyuria exceeding 5½ liters per day. Graham is unable to explain the increased amount and tension of the cerebrospinal fluid. In his case it increased enough to cause pressure in the hypophysial region and set up polyuria. Three of Maranon and Gutierrez's cases were treated by lumbar puncture with satisfactory results.

Concerning the therapeutics of diabetes insipidus, little need be said. The immediate effects of pituitary posterior lobe extract has already been mentioned. The effects are, however, only transitory and cease when the injections are discontinued or shortly thereafter. Lumbar puncture in some cases has had a salutary effect.

The only treatment outside of surgery that seems to be of permanent value is restriction of the sodium chloride and nitrogen contents of the food. When compression of the brain region in the vicinity of the hypophysis is manifest or suggested by symptoms, surgical operation would, no doubt, give relief, but the difficulty and the dangers of such surgery excludes its application except in very grave cases.

In syphilitic cases antiluetic treatment generally has had little effect upon the diabetic syndrome.

I am indebted to Dr. Jos. A. Capps and his associates for the privilege of using their records in the case reported.

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DISFIGURING SCARS—PREVENTION AND TREATMENT.

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In plastic surgery of the head or neck, it is essential to obtain a scar which is not disfiguring. Our observations in the French, English and American Hospitals during the war convinced us of

one fact, viz., that simple approximation of the skin edges invariably led to subsequent broadening and dimpling of the scar. Every plastic surgeon in the army has had the disagreeable experience of seeing some of his cases reoperated because of a disfiguring scar. Photographs made a month or so after the first operation showed a scarcely discernible scar. What occurs to cause this late broadening of linear scars and permits the disfiguring umbilications?

To understand this, it is necessary to review our knowledge of wound healing. In a clean aseptic wound where all the bleeding has been carefully controlled and the tissues are properly sewed in layers, we have immediately the production of a small amount of blood ooze which promptly clots. A few migratory corpuscles pass out into the clots and tissues. The fixed connective tissue cells and the endothelial cells of the vessels pass out and promptly multiply, forming embryonic tissue; these cells are known as fibroblasts. At this stage, we have the first splinting of the wound and the cut edges are held in accurate approximation. The fibroblasts destroy any leukocytes present and bridge across the tissues. From each side of the wound, new capillaries are formed; these pass through the clot, joining with their fellows from the other side. The fibroblasts later become spindle cells forming the interlacing fibers. This fibrous tissue formed is very contractile in type and soon obliterates the newly formed bloodvessels. If considerable oozing occurs, we may get the formation of the so-called coagulate lymph clot made up of blood clots, plasma clots, and leukocytes; the same healing process occurs later but the amount of fibrous tissue is materially increased and the extent of the scar is in proportion.

After healing has taken place in a wound approximated by a simple suture under tension, several factors enter into the alteration of the scar. In proportion to their activity, we may classify them in the following order: (1) Muscular pull; (2) contractility of the newly formed fibrous tissue; and (3) low grade infection. We are assuming that proper approximation has been made. If the skin edges are not promptly brought together, this will be a fourth factor in the disfiguring process.

In all wounds about the face or neck, the muscular pull is a potent factor to be constantly reckoned with. The incision as far as possible must be in the line of the muscle fibers. The fact that we have muscles inserting in the superficial fascia and even the skin itself must be considered. In making our closure, a margin of safety is allowed for this fact.

All newly formed scar tissue regardless of its location, contracts and in its early pliable condition is influenced by the muscle pull.

Low grade infection is a fairly rare process, thanks to our modern asepsis and Nature's bountiful blood supply in these areas. When it does occur, we cannot hope for a perfect scar.

Experience has shown us that the best method of preventing noticeable scar formation is to overcorrect as it were, at the primary operation. It is not sufficient to simply evert the skin edges; it is necessary to have accurate approximation of the superficial fascia and to bring fat to fat with the obliteration of all dead spaces. The use of the mattress suture with a skin coaptation button has been most satisfactory in our hands, as it permits us to obtain the conditions essential to proper scar formation.

FIG. 1

REPAIR OF OLD SCARS. When is the opportune time to resect an old scar? As long as the scar tissue is bright red, we know that the fibrous tissue has not finished its contraction, because when full contractility has occurred, the scar will be pale due to the obliteration of the capillaries. No scar should be repaired until

FIG. 2

this pallor exists. The surrounding tissues are then pliable and the scar may be excised. (Figs. 1 and 2.) The edges are undermined as shown in Fig. 3 and the edges are approximated by the mattress sutures with the use of the buttons. (Figs. 4, 5, 6, 7 and 8.)

A failure to use this everted skin-edge method where large flaps are used to repair defects will result in disfiguring scars. In flap

cases, it is necessary to evert the skin edges to a greater extent than in normal wounds as we have the shrinking of the flap itself to contend with.

FIG. 3

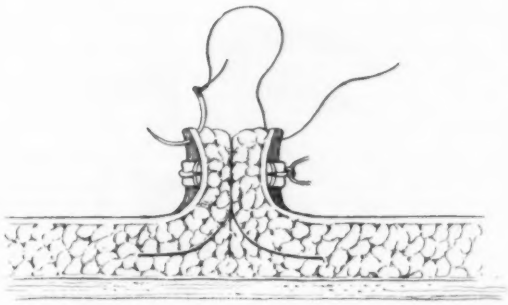

FIG. 4

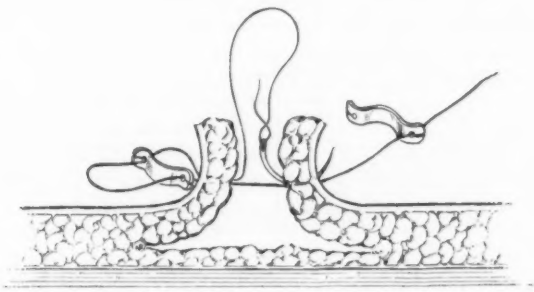

FIG. 5

FIG. 6

FIG. 7

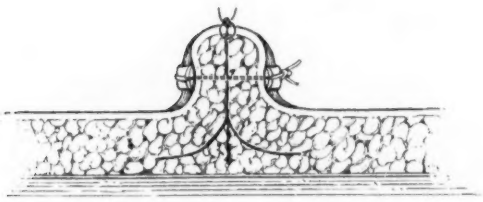

FIG. 8

Conclusions. 1. Eversion of the edges places subcutaneous tissue to subcutaneous tissue and as a result, less fibrous tissue is formed.

2. The overcorrected tissue after a comparatively short time will become flat and the scar will be scarcely discernible.

3. Muscular pull and the contractility of fibrous tissue are the most important factors in the production of depressed scars.

4. The use of a coaptation button with a mattress suture is necessary to obtain proper eversion.

5. The use of the button will obliterate all dead space and prevent blood clots' forming.

TRICHINIASIS, ENDEMIC AND SPORADIC, WITH A REVIEW OF THE PRESENT STATUS OF THE TREATMENT OF THE DISEASE.

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Although the diagnosis of trichiniasis can be made with absolute accuracy because of the distinctive laboratory findings, the milder cases of this disease frequently still remain undiagnosed. It is only after an eosinophilia is discovered that suspicion of a parasitic disease is oftentimes aroused. Only then are further studies undertaken which lead to an accurate diagnosis. It is the conviction of the writer that trichiniasis is far more common than is generally supposed and that a great many cases escape recognition.

The following case reports are submitted with the aim of drawing attention to the entire absence of clinical symptoms in some cases infected with trichiniasis, indicating the great ease with which instances of the milder types of this disease may remain undiagnosed.

The material is based upon observations made on an outbreak of the disease affecting 35 individuals and on 9 sporadic cases. In the endemic just referred to I had an unusual opportunity to not only make blood examinations on all the individuals known to have partaken of the pork, but to examine sections of muscles from a good number of individuals, including some that presented no clinical symptoms whatever.

Description of the Endemic. On January 15, 1920, a patient was admitted to the Waterbury Hospital with the possible diagnosis of typhoid fever. The patient was a married woman, aged thirty-one years, born in Italy, and six years in this country. The past history was entirely negative.

About two and one-half weeks prior to admission the patient commenced to suffer from indefinite abdominal pain, malaise and slight fever. The symptoms were apparently not very intense, since the patient was able to be up and about for a whole week.

At the end of that time the patient noticed that her eyes were quite swollen, and she also complained of slight soreness in various parts of the body, but particularly in the back. She also complained of considerable abdominal pain. A physician was consulted who prescribed for her and also examined her urine, but found neither albumin nor casts. The patient's temperature at the time of the doctor's first visit was 102° F.; pulse, 112; respirations, 20. The physican saw the patient twice subsequently. The edema of the eyelids had subsided considerably, but the muscular tenderness had increased. The temperature on one visit was 102.6°. On another visit it was 101.8°.

Upon physical examination at the hospital the patient was found to be a well-nourished and well-developed woman of middle age. There was evidence of slight edema of the face, particularly under the eyelids. The tongue was coated. The lungs were negative. The heart showed evidence of a slight degree of dilatation. Apex-beat was in the fifth interspace four inches from the median line. On auscultation a soft, blowing murmur was heard at the apex, but not transmitted to the axilla. The spleen was enlarged and was palpable two fingers' breadth below the costal margin. The uterus was palpable midway between the symphysis pubis and the umbilicus (the patient was about four months pregnant). There was a generalized body tenderness, particularly marked in the extremities. Because of the edema of the face and the muscular tenderness of the enlargement of the spleen a tentative diagnosis of trichiniasis was made. A history of eating pork was obtained, which still further increased the suspicion. A blood count was made immediately, with the following result: Leukocytes, 12,500; polynuclears, 60 per cent; lymphocytes, 3 per cent; mononuclears and transitionals, 5 per cent; eosinophils, 32 per cent. Next day a piece of muscle was excised from the gastrocnemius and trichinæ were found, which finding completed the diagnosis.

Upon further investigation it was found that the pork ingested by the patient was from an animal that was killed on their own premises. Some samples of the remaining pork were procured and trichinæ were demonstrated in abundance in various parts of the animal, particularly the muscles of the shoulder.

Further investigations of the case revealed the following: The animal was bought in August, 1919, kept for fattening and was killed on December 19, in early preparedness for a Christmas dinner. Two days after the animal was killed a party of 30 partook of the pork. According to the hostess the meat was roasted for about thirty minutes.

All except 3 of the people that partook of the pork that day have eaten of the same many times since, some of them daily. All the 3 that had eaten of the pork but once developed trichiniasis. All together, 40 individuals had partaken of the pork and 5 of

these evidently escaped infection; 35 showed evidence of greater or lesser infections as demonstrated by high eosinophil counts; 5 patients were severely ill and 1 of these succumbed to the disease.

TABLE I.—TOTAL AND DIFFERENTIAL WHITE BLOOD COUNTS OF THE PATIENTS THAT HAD PARTAKEN OF THE PORK.

No.	Name.	Age.	Sex.	Leukocytes.	Polynuclears.	Lymphocytes.	Mononuclears.	Transitionals.	Eosinophils.	Eosinophil myelocytes.	Basophils.
1	B. C.	31	F.	15,200	30	35	4	1	30		
2	L. C.	38	F.	12,800	40	30	5	4	20	..	1
3	Vil.	7	F.	14,600	28	58	2	4	8		
4	Fil.	1	M.	13,400	24	55	13	2	6		
5	D. C.	23	M.	5,800	64	30	5	1			
6	M. C.	36	F.	11,500	64	3	4	1	28		
7	Amb.	36	M.	7,600	62	33	3	2			
8	Mamie	35	F.	11,300	68	20	5	1	6		
9	A. L.	24	M.	6,100	78	20	2				
10	M. M.	34	F.	10,800	65	20	5	1	9		
11	L. M.	42	M.	9,500	47	33	4	3	12	..	1
12	J. M.	34	M.	13,100	39	12	8	4	37		
13	A. V.	8	F.	11,100	46	20	8	2	22	2	
14	M. V.	42	F.	9,400	64	20	2	2	11	..	1
15	Mike	5	M.	13,200	28	23	4	1	42	2	
16	Dan	7	M.	10,800	50	34	2	1	11	2	
17	John	38	M.	12,500	54	30	3	2	10		1
18	T. W.	59	M.	15,100	43	29	5	3	18	..	2
19	L. V.	11	M.	16,200	35	38	4	3	16	3	1
20	H.	22	M.	7,900	62	20	2	3	11	..	2
21	F. M.	17	M.	9,500	54	30	4	2	9	..	1
22	T. M.	25	F.	11,800	43	27	6	6	15	..	3
23	Jim	15	M.	14,100	38	31	5	6	19	1	
24	R. V.	7	F.	12,300	40	36	10	5	7	2	
25	G. M.	16	M.	16,200	50	31	3	5	10	..	1
26	D. V.	6	M.	12,200	42	26	6	3	20	3	
27	E. S.	17	M.	16,200	37	23	4	5	29	..	2
28	C. S.	9	F.	12,300	41	34	6	3	14	2	
29	R. S.	19	M.	12,000	50	21	4	5	18	..	2
30	M. S.	30	F.	7,600	49	24	5	4	17	..	1
31	Eddie	4	M.	10,700	31	26	7	6	27	3	
32	A. M.	6	M.	8,100	46	48	3	2	1		
33	Joe M.	11	M.	6,400	53	30	4	2	10	..	1
34	M. M.	8	M.	11,600	40	32	2	4	19	3	
35	F. M.	35	F.	14,100	52	28	1	6	10	..	3
36	Minn	1½	F.	12,600	16	54	3	2	21	4	
37	Marie	4	F.	9,100	38	44	3	3	9	2	1
38	Lor.	7	M.	12,400	38	48	2	2	8	2	
39	K. M.	24	M.	14,600	48	33	6	11	..	..	2
40	H. M.	40	M.	15,300	25	55	1	3	16		

The blood counts of these cases, along with the data of age, sex and so forth, are to be found in the accompanying tables (Table I). Thirty-five of the cases had an eosinophilia above 5 per cent. The

exact figures varied between 6 per cent and 42 per cent. Bits of muscles were excised from 2 of the patients with normal eosinophil counts and no trichinæ were found in either case. In the patients with the higher eosinophil values, the trichinæ were found in the muscles of 7 out of 8 cases examined. The triceps was used in every case.

TABLE II.—WHITE AND DIFFERENTIAL BLOOD COUNT IN THE FOURTEEN CASES OF TRICHINIASIS ANALYZED IN THIS PAPER.

No.	Name.	Leukocytes.	Polymorphonuclears.	Lymphocytes.	Mononuclears and transitionals.	Eosinophils.	Basophils.
1	J. M.	13,000	39	12	12	37	0
2	A.	17,600	52	13	5	29	1
3	B. C.	15,200	30	35	5	30	0
4	L. C.	12,800	40	30	9	20	1
5	O. D.	32,400	40	29	5	26	0
6	F. H.	28,200	41	10	7	41	1
7	R. C.	31,100	19	20	6	55	0
8	O. F.	26,400	20	14	4	60	2
9	G. F.	28,200	30	19	7	43	1
10	I. K.	30,600	23	20	6	51	0
11	S. K.	19,800	28	20	11	40	1
12	O. N.	12,400	41	18	5	36	0
13	F. L.	16,100	40	27	12	20	1
14	R. G.	10,600	53	23	9	14	1

All the cases that were not treated in the hospital, with the exception of 5 or 6, could not recall any untoward symptoms and had absolutely no complaints to make during the four weeks prior to this investigation. Of the 5 that had some complaints to make 4 had a recollection of a gastrointestinal disturbance of a very slight degree and for which none sought medical advice because it simulated attacks of indigestion that they had had before. Two of the patients complained of very slight muscular pains, which they attributed to a slight cold. None of them were sick enough to be confined to bed.

Analysis of Symptoms. For this purpose the clinical records and progress notes of 14 cases are used. Four of these belong to the endemic mentioned above. Of the 9 others there were 2 instances each of 2 members of a household being affected, and 5 cases where no other affected individuals could be traced or suspected.

Incubation Period and Onset. In only 2 cases of this series could the incubation period be determined with accuracy. Both these individuals ate of the slaughtered animal on the first day and did not partake of the pork since. In both cases the first symptoms appeared on the seventh day after the ingestion of the meat. With-

out any dietetic indiscretion to account for it they began to suffer with diarrhea. They also had epigastric distress and nausea, but did not vomit. Edema of the lids and face were noticed by both of these patients on the ninth day after ingestion of the pork.

The disease was ushered in by chilliness in 4 cases; by muscular pains in 6; by nosebleed in 2 and by edema of the face in 4 cases.

Symptoms and Signs. Fever: The patient's temperature varied from 101° F. to 105° F. A marked diurnal variation was quite common in the majority of cases. In 2 cases there was inversion of the usual evening rise, the highest temperature having occurred about 9 or 10 A.M. and the lowest in the evening. This condition persisted throughout the febrile period. In this series of cases the febrile period lasted from ten days to three weeks. A temperature of 106° F. was encountered but once and only lasted three hours.

Gastrointestinal: Dryness of the mouth and thirst were complained of by 11 of the patients. Three of the patients had a protracted diarrhea with traces of blood and mucus in the stools. Eight patients were markedly constipated, while in the remaining 3 the intestinal condition remained apparently normal throughout the disease. They all complained of some abdominal pain, especially during the second week of the disease.

Respiratory: Signs and symptoms of a mild bronchitis were present in 10 of the cases. Three of the patients complained of tightness of the chest, particularly in the presternal region. One case (which terminated fatally) had complete consolidation of the lower right lobe.

Muscular: Twelve of the cases here analyzed had distinct muscular pain and tenderness. In 7 cases it was most marked in the calves of the legs and in the thighs. In 3 cases it was distributed to almost the entire voluntary musculature; mastication was difficult; closing of the eyes was accompanied by a great deal of distress. In 2 cases the muscular pains were slight and inconspicuous.

Cutaneous: Edema of the face was present to a greater or lesser extent in 12 cases of the present series. In 3 of the cases it was very extensive; the face was swollen to unrecognizable proportions and the eyes were so swollen that the lids could hardly be separated. Subconjunctival hemorrhages were encountered in 4 cases, in 1 of which it was very extensive. Erythema was present in 3 cases. The same patients also showed dermographia and evidence of urticaria. Sweating was pronounced in 5 cases. It was most profuse during the second and third weeks of the disease. Pruritus and formication were distressing features in 2 instances.

Pulse: The pulse-rate showed no special changes from other febrile affections except in the striking persistence of arrhythmias in 3 instances. In 1 of these cases a pulsus bigeminus and trigeminus

made its appearance on the third day after admission to the hospital and persisted for six days. One patient exhibited three attacks of paroxysmal tachycardia in the course of two days. On one occasion the pulse was 210 per minute.

Heart: In the majority of cases here analyzed the heart showed no particular points of interest. In 1 of the cases the apex-beat was in the fifth interspace, 10 cm. from the median line. A soft murmur was heard at the apex and was not transmitted to the axilla. A systolic murmur, soft in character, was also heard at the pulmonic area. There was no history of rheumatism. This was the same patient that had the attacks of paroxysmal tachycardia described above. At the time of the patient's discharge from the hospital the murmur at the apex could no longer be heard, although the one at the base was still audible. The blood-pressure was not materially affected in any of the cases.

The spleen was definitely palpable in 4 cases. In 2 of the cases it was about 3.5 cm. below the costal margin.

Two of the patients in this series were pregnant women, 1 four months, the other two months. Neither one had miscarried.

Laboratory Findings. Urine: In 5 of the cases the urine was entirely devoid of pathologic elements. In 9 cases albumin was present; in 2 of these it presented a heavy cloud with the heat and acetic acid test. Casts were found in 4 cases, in 2 of which both hyaline and granular casts were present in great numbers. In 2 cases traces of sugar were found. In both cases it was apparently during the third week of the disease. The blood sugar was normal in both of these cases. The diazo reaction was done in 6 of the cases and was found positive in one instance. In this case there was evidence of profound toxemia.

Blood: The hemoglobin and erythrocytes were not appreciably affected in the milder cases but in the severe cases a marked secondary anemia was present. It became especially manifest toward the end of the third or during the fourth week of the disease. No nucleated reds were observed in any of these cases.

TABLE III.—RELATION OF THE EOSINOPHIL COUNT AND THE EASE OF FINDING THE TRICHINÆ IN THE MUSCLES.

No.	Trichinæ in muscles.	Eosinophils, per cent.
1	Abundant	42
2	Abundant	34
3	Very few	27
4	Moderate	14
5	Numerous	11
6	Moderate	19
7	Very few	30
8	Abundant	7
9	Only two parasites seen	28
10	Very few	16
11	Moderate	29
12	Abundant	6

The leukocyte count varied between 10,600 to 32,400. The accompanying tables indicate the details of the blood counts as well as the total and relative eosinophil counts. There was no relationship between the extent of the eosinophilia and the relative number of embryos found in the muscle specimens (Table III).

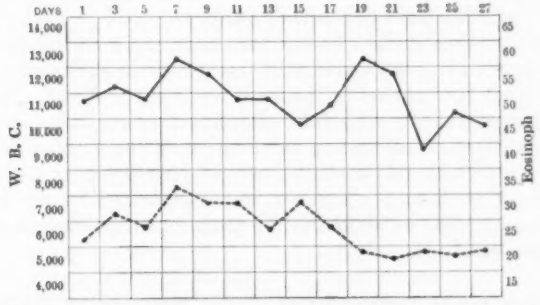

FIG. 1.—Relation of total white cell count to percentage of eosinophiles in one of the cases of trichiniasis.

Observations were made in 9 of the cases as to the persistence of the eosinophilia. (Fig. 1). In all but 1 it was still above 2 per cent at the end of three months. It reached a normal level in all the cases at the end of six months (Table IV).

TABLE IV.—DURATION OF EOSINOPHILIA IN NINE OF THE PATIENTS INVESTIGATED.

Name.	First month, per cent.	Second month, per cent.	Third month, per cent.	Fourth month, per cent.	Fifth month, per cent.	Sixth month, per cent.
J. M. . .	27	24	18	7	1	1
B. C. . .	34	29	20	14	7	0
M. C. . .	20	18	2			
E. S. . .	29	20	1			
M. M. . .	32	26	3	2	2	2
D. V. . .	19	12	5	1	..	1
A. M. . .	40	22	7	3	1	1
Lor. . . .	18	14	4	2	..	2
W. T. . .	56	9	7	1	2	1

Finding of the Trichinæ: The parasites were found in the muscles in every one of these 14 cases. In 2 cases, where excision of a piece of the triceps in the second week of the disease showed no parasites, positive results were obtained six weeks later. In several of the cases the embryos were found with no surrounding capsule. In other specimens, removed in the fifth week of the disease, a fibrous capsule was plainly evident. The connective tissue between

the muscle fibers was proliferated and the infected muscle fibers showed evidence of granular degeneration.

Trichinæ were found in the blood stream in 2 of 8 patients in which this search was made. In both cases it was in the second week of the affection.

The stools of all the cases were carefully examined for trichinæ but the parasites were not found in any.

Mortality: One of the 14 cases here analyzed terminated fatally (7 per cent). It was apparently due to the complicating lobar pneumonia. It occurred in the third week of the illness. Regretfully, the pneumonia was fully developed before first seen and the influence of the secondary infection upon the eosinophil count could not be observed, since the patient died the next day. The diagnosis of trichiniasis, however, was ascertained by the history of the case and was substantiated by finding free trichinous embryos in muscle specimens.

Summary of the Present Status of the Treatment of Trichiniasis. *Prophylactic.* This is still, and ever must be, the most important treatment of this disease. It may be considered under the following headings:

1. Inspection of meat.
2. Prevention of infection in hogs.
3. Proper cooking of pork.

The systematic microscopic examination of pork for trichinæ has been tried extensively in this country and in Germany, but it was given up as unpractical and uncertain. It was pointed out by Stiles and others that not only is the expense enormous and almost prohibitive, but that it did not seem to afford protection. During the years 1881-1898, when Germany had a very rigid method of microscopic examination of pork, there still occurred 2042 cases of trichiniasis with 112 deaths from meat that had been examined and released for trade as free from trichinæ. It illustrates how readily encysted trichinæ may escape detection.

Ransom,[1] of the Bureau of Animal Industry and of the Department of Agriculture, has carried out an extensive investigation on the effect of heat and refrigeration of trichinæ in meat, and has also investigated the efficacy of smoking, salting and other methods of preservation of meat.

The investigations of the various curing processes of meat have apparently not been completed. Inasmuch as smoking and salting would kill the trichinæ in the superficial layers only, it could not be depended upon to penetrate the deeper layers of the ham.

Ransom demonstrated that if a barrel of meat at 0° C. (32° F.) be put in a refrigerator at —15° C. (5° F.), it takes about seven days before the center of the barrel is at the same temperature as that of the refrigerator.

A temperature of —15° C. (5° F.) or below will destroy the trichinæ if exposed to it for about two weeks.

In view of these investigations the federal meat inspection authorities have adopted requirements that all pork that is to be used in the preparation of food products and consumed raw must be kept exposed to a temperature of —15° C. (5°) for at least twenty days or else it must be heated to about 60° C. (140° F.).

In connection with the heating of pork, Ransom has also pointed out the length of time it takes for heat to penetrate large portions of meat. In cooking a 15-pound ham in water at 180° F., it required two and a half hours to raise the temperature of the center of the ham from 78° to 137° F., and it required three and a half hours to raise the temperature of the center of the ham from 46° F. to 137° F.

The extermination of rats and mice near slaughter houses and hog-pens must be insisted upon. Examination of rats from slaughter houses has shown that at least 50 per cent of them are infected with trichinæ. Billings found all the rats from a slaughter house in Boston trichinous. Whether the rat or the hog is the normal host for the trichina has not been established. Staubeli believes that the hog is the normal host for the trichina. There is, however, no doubt but that infected rats help in continuing the infection among hogs. For the same reason hogs should not be fed on slaughter house waste or pork scraps and dead hogs. Rats and mice should be so disposed of that hogs could not come in contact with them.

The proper cooking of pork is the most certain and safest of all precautionary measures. One must remember, however, the length of time it takes for heat to penetrate to the center of a piece of meat. Ransom's observations on this point have been mentioned above. An ordinary sausage requires ten minutes' cooking in water at 71.1° C. (160°F.) to raise the temperature of the center of the sausage from 25.6° C. to 58.3° C. (78° F. to 137° F.) It is very evident, therefore, that pork is frequently insufficiently cooked, and especially when large hams are used one must be very careful that it should be heated sufficiently long for the center of the meat to be likewise affected.

All persons must be educated to the danger of eating raw or insufficiently cooked pork.

It has been pointed out that in the United States most of the local outbreaks of the disease can be traced to a small slaughter house or to a slaughtering of one or more hogs by a family for its own consumption or by a butcher for his own trade. Under such conditions the family or the buyers who partake of the meat get a large dose of trichinous material, while in the large slaughter houses the infected meat is very likely to be mixed with a great deal of meat from other hogs and the person partaking of the pork is not so apt to ingest a large quantity of trichinous material.

Medicinal Treatment. This is still unsatisfactory and is entirely symptomatic. The serum of animals convalescent from trichiniasis has been used with indifferent results. Salzer reported prophylactic and curative effects from such a serum, but Schwartz's investigations did not corroborate these findings. In 2 cases of the series reported in this paper I employed a serum from two individuals in which there was no doubt but what both had recovered from a mild type of the infection. I administered four injections in each case, each of 10 cc intramuscularly, at twenty-four hour intervals. There was no appreciable effect either on the temperature, the eosinophil count or on the duration of the disease.

If the patient is seen soon after eating the suspected meat it may be possible to abort the disease by gastric lavage, by administration of a cathartic and by giving fairly large doses of thymol. Two grains may be given four or five times in the course of the first twenty-four hours and followed by a cathartic.

Thymol has also been employed by intramuscular or subcutaneous injection. Booth reports good results from its employment in 1 case. He dissolved the thymol in sterile olive oil (0.65 gm. (1 gr.) of thymol in 1 cc of oil) and injected 2 to 3 cc subcutaneously or intramuscularly every day for seven days.

Glycerin, on account of its hygroscopic qualities, was recommended by Fielder, a tablespoonful every hour with laxatives. G. Merkel, of Nüremberg, has obtained good results with it.

Arsphenamin and other arsenicals have also been employed, but without any effect. I administered both old and new arsphenamin to 3 cases of trichiniasis, but observed no beneficial effects whatever.

No immunity is conferred by one attack of trichiniasis and no immune substances can be demonstrated in the serum of experimentally infected animals (Schwartz).

Summary. 1. A small outbreak of trichiniasis is reported affecting 35 individuals. Also 9 sporadic cases.

2. A clinical analysis is made of 14 of the more severely ill cases.

3. Blood and other laboratory findings are given with tabulations.

4. High eosinophil blood counts and free, unencysted trichina embryos were found in individuals that have partaken of the trichinous pork and yet have presented no clinical symptoms of the disease.

5. The author wishes to draw attention to the comparative frequency of the disease and to the great necessity of emphasizing the absolute importance of thorough cooking of pork.

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THE BLOOD IN MYXEDEMA*

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Although it has been recognized for many years that patients with myxedema may have an altered blood picture, this fact does not seem to be generally known. Doubtless, this may be explained by the lack of constancy in the blood findings, and also the difficulty frequently experienced in making a diagnosis of myxedema from the clinical picture alone. With the introduction of basal metabolism as a clinical test, and the observation that the metabolism is usually lower in myxedema than in any other disease, it is possible to make a much more accurate diagnosis of this condition than formerly. The syndrome of myxedema may be very vague and not infrequently it simulates other diseases, as for instance pernicious anemia. The metabolism likewise may be diminished in the latter disease, as shown by Tompkins, Brittingham and Drinker,[1] though the diminution is not usually as great as observed in myxedema. Inasmuch as the diagnosis of myxedema in each patient at the Peter Bent Brigham Hospital has been confirmed by the determination of the metabolic rate and the diagnosis made thereby as accurately as possible, it seemed worth while to report these cases with their blood findings.

Review of the Literature. In his original paper on myxedema, Gull[2] made no reference to the blood, but Ord,[3] three years later, stated that "the blood examined under the microscope appeared healthy." Four years after this (1881) Charcot[4] while delivering a clinic on myxedema expressed just the opposite view and remarked that those suffering from the disease were "anemic to a high degree," and Horsly,[5] in writing on the function of the thyroid gland, pointed out that marked anemia followed loss of the thyroid gland, and that the anemia included a reduction in the number of red corpuscles.

* From the Medical Clinic of the Peter Bent Brigham Hospital.

In 1888, the London Clinical Society's Report on Myxedema[6] stated that, "Allied with the fall in body temperature are changes in the blood. There is not only anemia due to loss of corpuscles but the relative proportions of these constituents are also altered . . ." However, this statement was based, in part at least, on experiments on cats in which the thyroid had been removed. As these animals later developed tetany the parathyroids were probably extirpated, thus complicating the picture. Nevertheless, 12 cases of myxedema with the blood findings were given at the end of the report, so that there were other grounds for their belief. Enough observations had been made by this time so that those interested in the condition recognized that an anemia was frequently a concomitant finding in myxedema, and in 1892 Putnam[7] wrote, "The point has not attracted as much attention as it deserves that the 'directly' hematopoietic functions of the thyroid, if they are of real importance, ought not to be met by ingestion of the thyroid secretion." From now on numerous cases with data on the blood findings are found recorded in the literature.

There does not appear, however, to be a uniform opinion concerning either the quantitative or the qualitative changes in the blood picture. Some writers[8] have reported normal blood findings; whereas others[9] have reported merely a mild anemia or simply that an anemia exists. Most observers[10]; have reported cases showing red blood counts ranging from 3,000,000 to 4,500,000 cells. Murray[11] in his excellent article on myxedema writes, "Examinations of the blood have shown that the number of red corpuscles may be reduced from between 4,000,000 and 5,000,000 (the average number in health) to between 3,000,000 and 4,000,000." However, lower counts than these occur and McCarrison[12] states that, "The reduction in the red blood corpuscles may amount to 2,000,000 or even to 3,000,000." Pitfield[13] a few years ago reported one case with a red blood count of 2,200,000 cells, and another with a count of 2,030,000 cells. The lowest red blood count found mentioned was in a case reported by LeBreton[14] in which the blood showed 1,750,000 cells per cu. mm.

A reduction of the hemoglobin has been observed which is usually greater in proportion than is the decrease in the number of red cells, so that a color index of less than one frequently obtains.

Falta,[15] Murray,[16] and Ewald[10]; agree that the hemoglobin may be reduced to 60 per cent, or even to 40 per cent of the normal. Howard[17] in discussing the blood in myxedema states that "The hemoglobin is found by most writers to be reduced 10 to 15 per cent below normal," and reports that in 12 cases in his series, "The hemoglobin was normal in 2, between 50 to 75 per cent in 8, and below 50 per cent in 2 cases." In one of Pitfield's[13] cases the hemoglobin was 25 per cent.

Just as the number of red cells appears to vary to a marked degree,

their characteristics do not seem to be well defined. In Mendel's[9] case the red blood corpuscles were somewhat smaller than normal; whereas, Kraepelin[8] and LeBreton[14] both found the diameter of the red cells to be increased, the former in spite of a normal count. V. Korczyuski[18] also noticed in one case that the red cells were abnormally large. In most cases, however, there has been reported little or no change in the appearance of the red cells, but this is not surprising in view of the fact that in most reported observations the anemia was of a mild grade. In those cases where the anemia is more severe, evidences of regeneration may be found. Pitfield[13] has found marked stippling of the red cells and other signs of basophilic degeneration. McCarrison[12] remarks that nucleated red blood corpuscles may be found, and Falta[15] goes so far as to say that "In many cases are observed erythroblasts." Minot,[19] who has given the best and the most thorough description of the blood in a case of myxedema states that "The red cells show a definite abnormal variation in size, though they average normal size. Cells slightly larger than normal occur; these are usually round, sometimes a trifle oval in shape, but large macrocytes are not seen. Microcytes are absent. Variation in shape is slight. The red cells stain fairly well, but they appear to be slightly achromic. Polychromatophilia rarely occurs, and the reticulated cells occur in normal numbers. No blasts or other red cell abnormalities are noted. The fragility of the red cells is not definitely abnormal."

All kinds of conditions have been reported as regards the white blood corpuscles. The report of the Committee of the Clinical Society of London[6] was that a "marked leukocytosis occurs." Ewald[10]; remarks, however, that in some cases there is a slight leukocytosis and Murray[16] has stated that "Except for an occasional leukocytosis the white corpuscles are normal in number and appearance." Leichtenstern[8] in a case of myxedema following extirpation of a goiter, found a leukocytosis with increase of lymphocytes. On the contrary, other observers have found a leukopenia of varying degree (Frey,[20]; Bence and Engle,[21] Kocher,[22] Mendel[9]). A third view is that of Howard[17] who believes that the "leukocytes are usually normal in actual numbers as well as relatively." Cabot's[10]; cases also showed the white cells to be normal.

The differential counts show little to go by, although as mentioned above, some observers have found either a relative or absolute lymphocytosis. According to Mendel,[9] Bence and Engle,[21] and Falta[15] the percentage of eosinophiles is said to be increased. On the other hand, Kocher,[22] found the number of eosinophiles to be normal and in Minot's[19] case no polynuclear eosinophiles were seen.

The basophilic cells have been usually reported as normal in number. Mendel[9] found them not to be increased. Kocher[22] found them usually from 0.2 to 0.4 per cent.

The coagulation time is said by Kocher[22] and Kottmans[23] to be decreased, by Bauer[23] to be increased.

As to the cause of the anemia, nothing is known. Horsly,[5] being impressed by the blood picture in cases of myxedema, considered whether the gland might not be a hematopoietic organ. Three years later the Committee of the Clinical Society of London[6] felt that the gland might be "concerned in hematopoiesis and not merely of corpuscles but also of the other elements of the blood." Putnam[24] thought it would be interesting to investigate "whether the cause of the anemia may not persist after the most striking myxedematous conditions have passed away." Nevertheless, little has been done to determine the cause of the anemia; although Esser[25] has found that after the removal of the thyroid in rabbits there was a decrease of myelocytes and an increase of lymphocytic forms in the bone marrow. Minot[19] has pointed out in his case that, "the anemia was apparently dependent upon a decreased formation of blood," and that "this decreased activity of the marrow is entirely consistent with the diminished activity of the other functions of the blood."

Presentation of Data. Fourteen cases of myxedema have been collected from the records of the Peter Bent Brigham Hospital. These represent the cases which through the history and basal metabolic rate* leave no doubt as to the diagnosis. Borderline cases have not been included. Unfortunately, no special studies were done on the blood, the routine examinations only having been made.

Of the 14 cases in the table, 3 had had no red-blood counts done. In the 11 cases in which red-blood counts were done, 3 of them (cases 2, 6, and 7) had essentially a normal number of red cells. Of the 8 cases with an anemia, the red-blood count varied from 4,070,000 to 2,280,000 of which 7 had a count of about 4,000,000 cells.

The hemoglobin was reduced in all the cases, varying from the highest value of 96 per cent to the lowest value of 65 per cent. In 4 cases (3, 5, 12 and 14) the color index was 1 or over. In 6 cases it was less than 1 per cent.

The white count varied from the highest recorded figure of 18,000 cells per cu. mm. to the lowest of 4,850 cells. It averaged about normal although it varied considerably on different days.

Assuming the normal differential count to be as follows:[26]

	Percentage.
Small mononuclears	20 to 25
Large mononuclears	3 to 5
Polymorphonuclear neutrophiles	65 to 75
Polymorphonuclear eosinophiles	2 to 4
Polymorphonuclear basophiles	0 to 0.5

* In obtaining the basal metabolism a 100-liter modified Tissot spirometer was used. After fasting from twelve to fourteen hours, the patient was given a thirty-minute rest period after reaching the laboratory, and the respiratory studies were begun only after the pulse rate had reached a level. Two periods were run in order to obtain a check. Gas analysis was done by Haldane Portable Gas Machines.

TABLE SHOWING CONDITION OF BLOOD IN CASES OF MYXEDEMA.

Case No. and initials.	Med. No.	Date.	Metabolism.	Hemoglobin.	Red-blood count.	Color index.	Remarks.	Smear.								Duration of disease in years.
								W. b. c., per cent.	Neutrophiles, per cent.	Lymphocytes, per cent.	Large mononuclears, per cent.	Eosinophils, per cent.	Mast cells, per cent.	Myelocytes, per cent.	Absolute number of lymphocytes.	
1. H. T.	5849	Jan. 2, 1917	−26	78	4,024,000	0.97	R.b.c. not remarkable	12,000	50	50	0	0	0	0	7400	?
2. G. L. F.	10390	Jan. 28, 1919	−34	94	4,976,000	0.95	Very slight achromia	18,800	67	29	4	0	0	0	5450	2½
		Mar. 2, 1919	−22	80	....	..	R.b.c. not remarkable	7,400	70	30	0	0	0	0	2239	
3. M. J. S.	11260	June 12, 1919	−33	90	....	..	R.b.c. not remarkable	6,600	56	35	4	5	0	0	2310	5
		July 22, 1919	−21	80	3,500,000	1.10	....	4,800								
4. C. T. B.	11541	Aug. 1, 1919	−30	90	....	..	R.b.c. not remarkable	10,000	83	9	6	2	0	0	900	?
5. T. B. F.	12227	Nov. 8, 1919	−34	80	4,070,000	1.00	R.b.c. not remarkable	6,000	60	33	2	3	2	0	1190	?
6. J. F. K.	12805	Jan. 28, 1920	−25	90	5,024,000	0.90	R.b.c. not remarkable	10,200	73	25	1	1	0	0	2521	?
7. K. O.	13295	Apr. 6, 1920	−38	90	4,730,000	0.95	R.b.c not remarkable	7,200	60	15	20	2	3	0	1080	13
8. M. J. B.	4192	Feb. 19, 1916	−49	82	....	..	R.b.c. not remarkable	6,800	61	30	8	1	0	0	2040	2
9. I. C.	11591	Aug. 9, 1919	−34	90	....	..	R.b.c. not remarkable	5,400	65	24	10	1	0	0	1296	5–10
10. D. A. M.	15672	Mar. 19, 1921	−40	70	4,016,000	0.87	R.b.c. not remarkable	6,400	62	35	3	0	0	0	2240	6
		Apr. 4, 1921	+ 1	75	4,280,000	0.88	....	7,100								
		July 6, 1921	−11	115	6,704,000	0.85	R.b.c. not remarkable	7,450	58	36	2	2	2	0	2682	
		Sept. 6, 1921	−20	98	5,472,000	0.90	R.b.c. not remarkable	9,400	67	21	12	0	0	0	1974	
11. J. F. B.	16697	Aug. 25, 1921	−32	68	4,144,000	0.82	Mod. achromia variation in size; slight poikilocytosis	9,900	59	29	9	3	0	0	2871	1
		Sept. 16, 1921	− 4	79	4,480,000	0.88	Slight achromia and slight variation in shape	9,200	64	22	14	0	0	0	2024	
12. S. H. V.	15108	Dec. 31, 1920	−38	65	2,280,000	1.40	R.b.c. not remarkable	7,900	65	32	1	1	1	0	2528	4
		Jan. 6, 1921	..	70	2,720,000	1.20	....	4,850	62	36	2	0	0	0	1746	
		Mar. 8, 1921	−16	80	3,004,000	1.20	R.b.c. not remarkable	5,800								
		Oct. 12, 1921	− 5	104	5,644,000	0.93	R.b.c. not remarkable	9,800	71	17	12	0	0	0	1660	
13. T. M.	16907	Oct. 5, 1921	−33	85	4,016,000	1.00	R.b.c. not remarkable	8,650	36	53	5	6	0	0	4594	4
14. H. T. B.	17359	Dec. 12, 1921	−35	80	3,950,000	1.00	Slight anisocytosis and poikilocytosis	5,600	76	20	4	0	0	0	1120	4
		Dec. 19, 1921	−21	83	3,000,000	1.30	Slight anisocytosis	5,600	64	36	0	0	0	0	2016	

1. Hemoglobin was estimated by the Tallquist method in the first 9 cases, by the Sahli method in the last 5 cases.
2. The duration of the disease was judged as well as could be from the history of the symptoms.

it is found that the polymorphonuclear neutrophilic cells fall slightly below the normal values in 9 cases.

The lymphocytes were normal in number in 4 cases (6, 9, 14 and 15) and decreased in 2 cases (4 and 7). Eight cases showed both a relative and absolute increase in the small lymphocytes.

The eosinophiles and basophiles seemed to be about normal.

In 11 of the cases the red blood cells were reported as normal. There was slight achromia in the remaining cases, in 2 of which slight anisocytosis and slight poikilocytosis were also reported.

A study of the table reveals no relationship between the degree of anemia and the metabolic rate. Likewise there appears to be no relationship between the degree of anemia and the duration of the disease. However, it is difficult to place the onset of the disease, as the symptoms begin so mildly.

Following treatment the anemia tended to disappear as is well shown in Case 12 which has been studied more completely than the others.

Conclusions. 1. The blood picture associated with myxedema is not constant and there are no changes which can be cited as typical of the disease. Usually, however, there is a moderate secondary anemia.

2. The hemoglobin is usually reduced.

3. The white blood corpuscles average about normal but tend to vary with the red-blood count.

4. The differential count usually shows the polymorphonuclear neutrophiles to be somewhat decreased in numbers. The lymphocytes may show a relative or absolute increase.

5. There is no relationship between the degree of the anemia and the duration of the disease or the metabolic rate.*

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CANCER OF THE COLON.*

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The management of cases of cancer of the colon has been a serious problem for generations. In 1716 Pillore of Rouen made use of an artificial anus in the treatment of cancer of the rectosigmoid; Fine of Geneva, in 1797, followed his example. The first successful resection of the pelvic colon for cancer causing obstruction was performed by Reybard, in 1833. Ten years later this operation caused a storm of controversy in the Paris Academy of Medicine, and was rejected by the leading surgeons of the day as too dangerous. Although this operation marks the first step in surgery of the pelvic colon, no less than forty-two years elapsed before the record case was reported by Thiersch who, in 1875, resected the pelvic colon for cancer and the patient died. About the same time, in 1879, Gussenbauer successfully removed the iliac flexure of the colon, in a man of forty-six years, and operated with good results in other cases. Radical treatment for cancer of the colon was soon attempted by a number of surgeons, notably Péan, Guyon, and Nélaton, but the alarming mortality discouraged further attempts along this line of intervention, and colostomy remained the procedure of choice in these cases. It was about 1880 before resection became a recognized procedure in surgery of the large intestine.

The technic of colectomy was modified by Volkmann in 1883 by the application of permanent colostomy. Nine years later, Bloch of Denmark described his procedure of resection for cancer in three stages. His work became better known through the contributions

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of Mikulicz. Results improved at once, but these two methods were not considered the last word in surgery of the colon and, about this time, numerous suggestions were made concerning a better technic of resection and intestinal suture, until enteroanastomosis finally constituted decided progress in the management of cancer of the colon.

The first total extirpation of the rectum for cancer was performed by Lisfranc, in 1826, who utilized the perineal route. Because of grave septic complications, this procedure was soon abandoned in favor of palliative measures such as formation of an artificial anus or rectotomy. However, the value of Lisfranc's procedure was gradually recognized; the operative technic was modified by Denonvilliers, who added to it a posterior longitudinal incision. From 1864 to 1884, several successful resections were reported by French and German surgeons with variable results. However, opinions were widely divided; in England the method of choice was lumbar colostomy. About this time, Kraske recommended the sacral route, a method which extended the surgical indications and under otherwise favorable conditions permitted more or less restoration of function. The results of this method, however, did not entirely meet expectations; some years later, they were investigated by Koenig, and a mortality of 33 per cent, with many recurrences, was shown. In spite of improved technic, Kraske's operation still remains a serious procedure. Excision of the cancerous segment has since become the operation of choice, the surgeon having at his disposal a variety of routes, according to the requirements in a given case, namely the perineal, the perineococcygeal, the sacral, or the abdominoperineal.

From the statistical point of view, it is usually estimated that the relative frequency of gastro-intestinal cancer is equivalent to 50 per cent of cancer in general, while about 16 per cent of the cancers of the digestive tract occur primarily in either the rectum or the sigmoid flexure of the colon. The various segments of the colon are involved as follows: Ascending colon in 11.6 per cent, hepatic flexure in 6.4, transverse colon in 10.2, splenic flexure in 4.9, descending colon in 7.1, and sigmoid flexure, in 27.3. The prognosis is largely governed by the location of the cancer; it is especially unfavorable in cancer of the sigmoid and splenic flexure. A recent report from Hochenegg's Clinic, comprising 779 cases in the last fourteen years, shows that cancer of the rectum represented about 16 per cent of all cases of cancer in the hospital. 44.8 per cent of these cancers were in the ampulla and 25.9 per cent were at a distance of 10 cm. from the sphincter. According to older literature, Boas found, among 500 cases of cancer of the digestive organs, 83 of cancer of the rectum.

Etiology. Local irritation undoubtedly plays an important part in the etiology of cancer in general and of cancer of the colon in particular. The colon is constantly exposed to contamination from

stagnating intestinal contents, which may, on good grounds, be suspected of harboring the living cause of cancer. Ochsner has called attention to the alarming frequency of cancer of the stomach in what he picturesquely describes as "manure eating people," meaning the consumers of raw vegetables grown in soil fertilized with barnyard manure and so forth. The question arises if the popular demand for uncooked green vegetables and salads, a by-product of the vitamin controversy, is in part responsible for the increased cancer mortality of the last few years. The increase in occurrence of cancer from the cecum to the rectum, and the predominance of cancer in the anorectal region, is readily accounted for by the common presence of local irritative factors. Heredity as an etiological or rather as a predisposing factor has been considered as an important element, but this view has been discredited. Apparently it played no part in any of the cases of cancer of the colon and rectum in the series of 10 cases herein reported.

Location. Since May, 1919, 10 cases of cancer of the colon have come under my observation. The cancer was in the cecum in 1 case, in the transverse colon in 1, in the splenic flexure in 1, and in the descending colon in 1; in the sigmoid flexure in 2 cases, and in the rectum in 4 (2 growths were in the true anus and 2 were in the lower pelvic colon).

Report of Cases. CASE I (St. Vincent's 4489–20) A woman, aged forty-eight years, suffering from cancer of the cecum, complained of indefinite symptoms of biliary and cecal colic.

At the operation, it was found necessary to remove the cecal coil on account of cancerous obstruction of the ileocecal valve. The infected gall-bladder, which contained stones and whose fundus appeared cancerous, was also removed. This was later shown to be cancer. Death resulted four days later from cardiovascular collapse concomitant with acute gastric dilatation.

CASE II (St. Vincent's 887–21). A woman, aged sixty-five years, with cancer of the transverse colon had symptoms of incomplete intestinal obstruction, and was kept under observation four days after the acute obstruction had been relieved by enemas.

In this case, the roentgen-ray findings were quite indefinite. The physical signs were variable distension of the right colon, definite borborygmus, and persistent recurrent attacks of intestinal colic. There was no palpable tumor. Under the diagnosis of chronic intestinal obstruction, the patient was operated on, March 16, 1921, and a cancer of the transverse colon found. This was resected and an end-to-end anastomosis made. The patient recovered uneventfully and is now in good health.

Case III (St. Vincent's 3372–20). A man, aged thirty years, with cancer of the splenic flexure, had been operated on twice within two years before I saw him, once for appendicitis and once for adhesions around the cecum. He complained that the symptoms he had had prior to the operation for adhesions persisted, but with predominance of pain in the region of the splenic flexure and left kidney.

The simulation of renal pain necessitated urological examination, in order to exclude renal disease. The findings demonstrated the kidney to be normal, while roentgenograms of the colon were indefinite with regard to obstruction. However, in view of a palpable mass, the persistent colicky pains at the splenic flexure, and the clinical dilatation of the transverse colon and cecum, a diagnosis was made of chronic intestinal obstruction at the splenic flexure.

Operation was performed April 8, 1920, through the left upper abdominal route, and consisted in resection of the splenic flexure, which contained carcinoma. Much difficulty was experienced owing to ankylosis of the splenic flexure by excessive adhesions. A side-to-side anastomosis was made after mobilization of the descending colon with satisfactory results. The patient recovered uneventfully, has gained 30 pounds in weight, is free from all signs of recurrence, and is able to continue his work as my chauffeur.

Case IV (St. Vincent's 4056–21). A woman, aged thirty-five years, with cancer of the descending colon came under my observation complaining of colicky pain in the lower left quadrant of three weeks' duration. She had had intermittent diarrhea, and had lost weight for the last five months. Roentgenograms revealed a defect in the descending colon just above the crest of the ileum suggestive of malignancy.

At operation, November 2, 1921, a carcinoma of the descending colon was found and resected, followed by suture anastomosis. Although an advocate of a two-stage operation, I performed a resection on this patient, because of the short history of obstruction, and because, during mobilization, a small perforation was discovered on the lateral wall close to the mesentery. Usually, however, when there is a history of more or less complete and prolonged obstruction, I prefer the two-stage operation. This patient is alive and well.

Case V (St. Vincent's 2074–19). A man, aged seventy-three years, with an acute perforation through a cancer of the sigmoid was seen in emergency. He had had attacks of intestinal colic and diarrhea for eighteen months. A tumor was palpated in the lower left quadrant.

Operation, May 21, 1919, revealed a large cancer of the sigmoid with perforation on the outer wall. This was mobilized and brought out on the abdomen as a colostomy. Ileostomy was also immediately performed. Death occurred on the fifth day from general peritonitis.

CASE VI (St. Vincent's 426–22). A woman, aged seventy-six years, had an obstructing cancer of the sigmoid flexure. She had had symptoms of intermittent obstruction and progressive starvation for two years, and had been under medical treatment for colitis for eighteen months.

No attempt was made to remove the tumor. Colostomy was performed to relieve the symptoms. Death occurred in six days from starvation, and cardiac collapse.

CASE VII (St. Vincent's 2230–20). A man, aged forty-six years, who had been treated elsewhere for hemorrhoids for one year was referred to me because of a growth in the anus, which proved to be cancerous.

Exploration revealed a metastatic nodule in the right lobe of the liver, and radical removal of the growth in the anus was not attempted. A permanent colostomy was performed.

The patient survived the operation one and a half years with a fair degree of comfort, and died from general carcinomatosis.

CASE VIII (St. Vincent's 3671–20). A woman, aged thirty-nine years, came for consultation on account of diarrhea, anal pain, and tenesmus, of six months' duration. Inspection revealed a small ulcerating growth at the margin of the anus, infiltrating the sphincter muscles and narrowing the lumen of the gut, so as to prevent digital examination. The abdomen was greatly distended, and the patient vomited repeatedly. A slight amount of flatus was finally obtained through the anus by means of a small rectal tube, which considerably relieved the distention.

On the third day, exploratory, laparotomy and permanent colostomy were performed as a first stage. Because of the marginal location, and apparent spreading of the carcinoma into muscles, the patient was subsequently referred to the General Memorial Hospital for intensive radium treatment. She was last seen six weeks ago at which time the colostomy was working well and she was quite comfortable. However, further infiltration of the carcinoma into the perianal region had occurred. Because of the absence of pain, the patient is anticipating ultimate recovery.

CASE IX (St. Vincent's 1224–21). A woman, aged sixty-three years, was referred to me because of chronic intestinal obstruction, rapid loss in weight, and a foul discharge from the anus for one year. A palpable mass could be felt on vaginal examination, and a diagnosis of cancer of the true rectum was made.

Abdominal exploration and a permanent colostomy were performed as a first stage. The growth was mobilized in anticipation of removal later. The patient died on the sixth day from peritonitis.

CASE X (St. Vincent's 4981–21). A woman, aged fifty-eight years, was brought to the hospital on account of intestinal obstruction and starvation. A mass in the iliac region extending into the pelvis was palpated. A colostomy was made, and the patient died two weeks later. Extensive metastasis was discovered at necropsy.

Discussion. In reviewing these cases with special reference to diagnosis, it is noteworthy that 1 of the 10 patients had been operated on under the diagnosis of appendicitis. The experience is by no means uncommon, and irritation from obstruction in the colon may actually lead to infection and inflammation of the appendix, as recently pointed out by Beall, whose patient clinically had appendicitis, probably induced by the back pressure of the fluids in a chronically obstructed cancerous colon. The excised appendix was swollen, congested, and contained an excess of fluid in its lumen.

My observations also confirm the well known fact that malignant tumors of the large intestine have a tendency to remain latent for a long time, the function of the bowel apparently remaining undisturbed by the existence of a growth in one of its segments until obstruction actually supervenes. This period of latency may be very protracted; Mikulicz estimated it as lasting from six months to three years and claimed that cancer of the colon first manifests itself clinically by its complications in the form of stenosis, ulceration, and hemorrhage. Occlusion is likely to supervene abruptly, without prodromes, often without progressive aggravation of symptoms. Cancers of the sigmoid flexure and cancers in the rectum sometimes cause sudden obstruction through enterospasm, edema, or invagination, usually preceded by obstinate constipation. In many instances, during the stage of incomplete obstruction, endoscopic examination, may reveal the obstacle to be a slightly protuberant, more or less infiltrating carcinoma. The entire colon can be readily filled with the barium enema, unless the enema is prevented from passing beyond a given obstacle and in this event the seat of obstruction will reveal the focus of the disease.

Roentgenograms are usually the best means for determining the exact location of a cancer of the colon. But in early cases the diagnosis must be made exclusively on the basis of functional disturbances, such as flatulence with colicky pains, diarrhea alternating with constipation, local tenderness, and increased discharge of more or less offensive mucus. The passage of blood is noted earlier in the disease in proportion to the propinquity of the cancer to the anus, on account of injury of the growth during defecation. It is noteworthy that certain cases of cancer of the colon present a more or less distinct picture of renal colic; this was typical of my cases, and indicates the diagnostic advantages to be derived in obscure cases of this description from a carefully conducted urological examination.

Nearly all the segments of the colon are accessible to systemic

palpation so that the tumor, its shape, size, and mobility may be often ascertained in favorable cases. Two important sources of error are certain renal tumors, and intermittent segmentary contractions of the bowel, which apparently increase the circumference of the cancer. Bimanual palpation is especially valuable in cancers of the pelvic colon. Percussion and auscultation are serviceable for the detection of local tympanities or incipient dilatation of the cecum, a valuable early sign of stricture lower in the gut. Digital exploration of the rectum, and rectocolonic endoscopy, are among the most useful measures at our command, permitting biopsy and catheterization of the colon in suitable cases. The recognition of cancers of the rectum is based on inspection of the anus, proctoscopy and sigmoidoscopy, vaginal examinations in women, and sometimes cystoscopy.

General Characteristics of Cancer of the Colon. Cancer of the ascending colon and hepatic flexure may be movable or adherent, elongated, or round and nodular, and may develop insidiously or fairly rapidly. Small cancers of the hepatic flexure are usually not palpable; larger growths are likely to extend backward and are more easily discovered. These growths must be distinguished from renal tumors and retroperitoneal neoplasms in general, as well as from tumors of the liver and gall-bladder. Cancers of the transverse colon are more superficially situated, more accessible to palpation, and often more freely movable than the foregoing. Such growths may be found in the vicinity of the stomach or low down toward the pelvis, so that confusion may occur. The splenic flexure and adjacent descending colon are fairly common and well concealed seats of cancer of the colon. The intestinal coil here lies at a greater distance from the anterior surface of the abdomen than any other segment of the colon, and the majority of these cancers remain small, while the other manifestations are not always well marked. The growths become palpable only after they have reached a certain size, or if the splenic flexure occupies an abnormally low position. Under these conditions the findings may suggest tumor of the spleen, kidney, or omentum. According to Madelung, such cancers, because of their anatomical relations, are especially likely to cause intestinal obstruction. With cancers of the sigmoid flexure, the most common in order of frequency, stenosis very often promptly manifests itself by colics, obstipation, and sometimes tenesmus. Large or medium-sized tumors often lie as fairly movable masses in the lower abdomen and may extend as far as the umbilicus, while small hard growths cannot be palpated as a rule. Rectal prolapse is not infrequently noted in the presence of small cancers of the sigmoid flexure, further invagination being prevented by the increasing dimensions of the cancer.

A suspicion of cancer of the colon usually leads to its detection. In the interest of the patient, it is urgently desirable to handle all

doubtful conditions as possible malignancies, unless a more harmless cause of the existing disturbances has been positively ascertained. The results of timely operative procedures for cancer of the colon are superior to results of treatment of cancer of any other organ, with the possible exception of cancer of the body of the uterus. Lymphatic involvement is fortunately long delayed, and more or less marked clinical manifestations appear in most cases long before the tumor has become inoperable. The inefficiency of radiation as compared to surgery in the treatment of malignancy of the colon and rectum is illustrated by recent observations in the Vienna Clinic, where roentgen-ray and radium treatment yielded no benefit; in all but 1 of the 28 cases in which it was utilized it seemed to be injurious rather than helpful in its effect on the disease.

According to recent findings of Schoemaker, the operative mortality of cancer of the colon in a large clinic amounted to 6 of 46 cases (13 per cent); 4 of these operations included resection of the colon. Of 30 patients operated on in Utrecht 6 died (20 per cent). In Schoemaker's personal experience, 2 of the 32 patients (6 per cent) died as a result of the operation. The localization of the growth concerned the first segment of the ascending colon, or the terminal segment of the descending colon. Numerous patients were operated on in a stage of acute ileus, others in chronic ileus. The youngest patient was aged forty-four years and the oldest was eighty-four.

Treatment. For a long time, the treatment of cancer of the colon remained palliative, in the form of an artificial anus, for the relief of obstruction, the most common complication of these cases. The remarkable advance of abdominal surgery in general, and the improved technic of intestinal operations in particular, led to resection, in one stage, of the tumor as well as of the affected glands; but the imperfect results soon showed the necessity of two-stage or three-stage operations, which were almost exclusively utilized until a further, and almost phenomenal development of operative technic permitted the resumption of radical treatment in one stage. However, although less brilliant for the surgeon and involving the inconvenience of a temporary artificial anus for the patient, two- or three-stage operations are undoubtedly safer and for this reason preferable in the great majority of cases.

Colectomy in one stage aims at extensive resection of the tumor-bearing segment and its mesentery which, after liberation from adhesions and mobilization of the colonic segment, are removed like a sac with the septic contents. The resection is immediately followed by an end-to-end or side-to-side anastomosis. One-stage colectomy, according to Boyer, is the operation of choice on the right side, whereas two-stage or three-stage operations are indicated on the left segment of the colon. The one-stage colectomy is definitely contraindicated in all cases complicated by intestinal obstruction.

The greatest cause of failure, after primary or secondary one-stage colectomy, is peritonitis. This is due: (1) to the extreme sepsis of the intestinal contents, (2) to the exposure to infection of the raw surfaces created by the detachment of the colonic wall, (3) to some extent, to the technical difficulty of suture application, as well as to the endangerment of the sutures by the passage of hard scybala, and (4) to the peculiarities of the local blood supply.

The adherents of one-stage colectomy consider the cancer to be operable during the entire period of latency, which may extend for from several months to three years, before clinical manifestations occur. The surgical indications for radical interference are therefore governed by a careful anatomical and clinical study of the syndrome. One-stage colectomy often becomes the treatment of choice during the period of tolerance, so that the essential point really is the determination of the most suitable time for the operation. But the clinical findings, as a rule, furnish only more or less indefinite operative indications during the entire period of latency, and an incipient cancer can be revealed only through exploratory laparotomy. This should be performed before the onset of intestinal obstruction, as soon as the patient seeks advice for obstinate constipation, which is accompanied by loss of weight and abdominal pain, alternating with attacks of diarrhea. The greater number of patients come under observation with long standing cancer and stricture, and when first seen are in a state of chronic obstruction or occlusion. In these circumstances two-stage colectomy is distinctly and necessarily indicated. One-stage colectomy, while undoubtedly the ideal procedure, depends for its justification on a timely diagnosis, the essential condition for a safe, rational and radical operation for malignant conditions of the colon.

Technic of Operation. Cancer of the pelvic colon may be treated by several operative procedures; namely, resection of the tumor, reëstablishment of the passage, and suture of the abdominal wall in one stage; resection of the cancerous segment with suture of the afferent and efferent ends into the abdominal wound in another stage, followed later by closure of the resulting artificial anus; or exposure of the affected gut in one stage, resection in the second stage, and closure of the artificial anus in the third stage. According to Schwartz, in Paris, the latter method in three stages is the procedure of choice. The only indication for operation in one stage is an excellent condition of the intestine, which guarantees good anastomosis, but this condition is very uncommon. In all cases in which the gut can be mobilized, it should be exposed; only when this is not practicable, may resection be performed at once, with, or sometimes without, fixation of the two ends in the wound. In order that healthy tissue may be operated on at the second stage, it is of course necessary to mobilize and extensively displace not only the tumor, but also the mesocolon, so as to prevent the tumor from being drawn back into the abdominal cavity by the intestinal mass.

From the operative viewpoint, the sigmoid flexure of the colon presents a segment of bowel extremely well adapted to resection. Being a long organ with a well developed mesentery, which can be drawn out of the abdominal cavity, it offers all the conditions required for surgical interference under favorable prospects. The essential point is the timely recognition of the cancer in this region, before the occurrence of obstruction, adhesions, and glandular involvement. The extirpation of the cancer in one stage is entirely feasible, and under these conditions has a fairly low operative mortality.

The principles which may be considered in the basic technic of the one-stage removal of these cancers are: (1) adequate abdominal incisions, (2) proper mobilization of the diseased segment to insure a serviceable anastomosis without tension, (3) preservation of adequate blood supply to the distal segment, and (4) formation of an efficient end-to-end or lateral anastomosis. However, since experience shows that these cases seldom come to operation early, the two-stage or three-stage operation is the one of choice.

Mortality. Cancers of the terminal sigmoid, as pointed out by W. J. Mayo, cannot be separated surgically from cancers of the upper rectum, on account of the marked tendency for cancer of the sigmoid to invade the rectum, and *vice versa*. In the Mayo Clinic from January 1, 1893 to December 31, 1915, the histories of 753 patients suffering from cancer of the rectum and rectosigmoid were recorded, and 430 of the patients were subjected to radical operation. The operability of the cancers, at the time when the patient was first seen, amounted to 53.1 per cent in the earlier cases, as compared to an operability of less than 25 per cent in the experience of Harrison Cripps (1913) and was subsequently increased in the Mayo Clinic to 71.8 per cent owing to the routine performance of a radical operation in extensive cancers, provided extirpation was not prohibited by the involvement of vital structures. Next to this cause of inoperability, ranked (1) metastasis of the liver, (2) peritoneal retroperitoneal metastasis, and (3) glandular metastasis. According to more recent data, the mortality of the radical operation in the Mayo Clinic averages about 10 per cent. The important causes of operative mortality, as stated by Mayo, who points out that a low mortality is coincident with a low operability, are in order of frequency, sepsis, nephritis, undiscovered metastatic tumors, hemorrhage, postoperative intestinal obstruction and exhaustion.

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REVIEWS.

MANUAL OF GYNECOLOGY. By JOHN OSBORN POLAK, Professor of Obstetrics and Gynecology, Long Island College Hospital, New York. Second edition. Pp. 396; 139 engravings; 10 colored plates. Philadelphia and New York: Lea & Febiger, 1922.

IN revising this manual the author has rewritten entirely some of the chapters and has added many new illustrations from specimens in his collection. It describes the lesions of the female generative organs, omitting irrelevant subjects, and stresses pathology in ample manner, with the result that a remarkably large amount of information is condensed in a small volume, though rhetoric has been sacrificed ruthlessly at times. The book's essential characteristic is the expression of the opinion of a progressive leader in the profession on debatable points, and the presentation of his treatment of gynecologic diseases with a properly detailed description of his technic in the common operations. L.

A MANUAL OF DISEASES OF THE NOSE AND THROAT. By CORNELIUS G. COAKLEY, A.M., M.D., F.A.C.S., Professor of Laryngology and Otology in the College of Physicians and Surgeons, Columbia University, etc. Sixth edition, revised and enlarged. Pp. 635; illustrated with 145 engravings and 7 colored plates. Philadelphia and New York: Lea & Febiger, 1922.

THAT this manual of diseases of the nose and throat by Prof. Coakley has now come to its sixth edition, is evidence of the favorable consideration which it has received at the hands of the medical profession. Prof. Coakley is himself preëminently a clinician and skilful surgeon and it is the clinical and surgical aspect of this book that makes it of distinct value to the laryngologist. The chapters on sinus disease give a very admirable portrayal of the methods of diagnosis and treatment. He is conservative, yet at the same time radical in his suggestions, when radicalism is indicated. In fact, throughout the book where operative procedures are considered, the subject is exceedingly well handled. On the other hand, the

anatomical considerations are too brief to be of any especial value, and the treatment of pathology is not as reliable and up to date as we would like. The book, however, would make a valuable addition to the laryngologist's library. W.

SELECTED WORKS OF THOMAS SYDENHAM, M.D. By JOHN D. COMRIE, M.D., F.R.C.P., EDIN., Lecturer on History of Medicine and on Clinical Medicine in the University of Edinburgh. Pp. 153; 4 illustrations. New York: William Wood & Co., 1922.

IN this small and relatively inexpensive book are combined a brief life of "the prince of English physicians" and extracts from his published works. The selections have been very intelligently chosen and one finds at least a part of each of those which have made the name of Sydenham familiar to all. Among those included are the well-known observations on St. Vitus's dance, gout and on the use of Peruvian bark. No history of medicine nor biography can be a satisfactory substitute for familiarity with a great man's original writings. Unfortunately such works are seldom available in convenient form. Publications such as the present one should be encouraged and should be of interest to both students and practitioners. P.

OPHTHALMOSCOPY, RETINOSCOPY AND REFRACTION. By W. A. FISHER. Pp. 218; 248 illustrations. Chicago: W. A. Fisher, 1922.

THIS book is written for the general practitioner, to give him a working knowledge of ophthamoscopy, retinoscopy and refraction. Some exception might be taken to a statement in the introduction that ophthamoscopy and the fitting of glasses belong to the general practitioner The author describes a schematic eye in which lenses can be inserted anteriorly and pictures of the fundus posteriorly, with a shutter diaphragm in front of the lens, to serve as a pupil. It can be made emmetropic, hyperopic, or myopic, and can be used as a human eye for practice in obtaining the fundus reflex, and for learning to recognize fundus details. Retinoscopy and refraction are covered in as full a manner as is possible in a book of this scope, giving the essential fundamentals and methods of making the various examinations for determining the proper glasses to be prescribed for a patient. Attached to the end of the book is a small atlas of 24 colored plates of the fundus, depicting the normal and some of abnormal conditions seen in routine examinations. S.

THE HEART AS A POWER CHAMBER, (a Contribution to Cardiodynamics). By HARRINGTON SAINSBURY, M.D., F.R.C.P., Consulting Physician to the Royal Free Hospital and the City of London Hospital for Diseases of the Chest. Pp. 248; 22 illustrations. London: Henry Frowde, Hodder & Stoughton, 1922.

RELATIVE to the anatomy, physiology, and pathology of the cardiovascular apparatus, the author discusses certain known facts, and speculates upon "the design and foresight which these reveal." The pages present an endeavor to show how these facts "disclose the living principle, the Archæus, working within the organs and tissues." The author's observations upon the relative weights of the muscular walls of the four chambers of the heart comprises his original contribution, and his views regarding the mechanics of the aortic valve, his most interesting presentation. The book as a whole leaves much to be desired; especially are the chapters on heart failure and treatment inadequate. A.

GREEK BIOLOGY AND GREEK MEDICINE. By CHARLES SINGER, University College, London. Pp. 128; 8 illustrations. Oxford: Oxford University Press, American Branch, 1922.

THE medical historian will be very much interested in this small volume on the evolution of Greek biology and medicine. It is a series of essays by one who is a student of Greek and the early Grecians, and can be recognized as authoritative. It is very well written, has a tremendous amount of information and is compressed into a comparatively few pages. M.

REPORTS OF ST. ANDREWS INSTITUTE FOR CLINICAL RESEARCH. Vol. I. Pp. 208; 54 illustrations. London: Oxford Medical Publications. Henry Frowde, Hodder & Stoughton, 1922.

IN this volume is assembled the first collection of reports from St. Andrews Institute, recently founded by Sir James Mackenzie. The aims and methods of research of the Institute are set forth by Mackenzie and other members of the staff. In addition, there are a number of special articles, including a valuable study of cutaneous sensibility by Waterston. The noval research initiated by Mackenzie, and being carried out with the aid of a staff of specialists and the entire medical personnel of the city of St. Andrews, for the purpose of carefully studying, recording and

analyzing all available clinical material in the city, promises valuable results. St. Andrews was chosen for the experiment partly on account of the non-migratory character of the population. It is hoped, therefore, that the records will become increasingly valuable as a source of reliable data bearing on the factors predisposing to disease and the earliest symptoms of disease. The chief merit of this volume lies in the fact that it describes the plan of a splendid research. For the results, we shall have to await future reports. W.

DISEASES OF THE HEART: A HANDBOOK FOR STUDENTS AND PRACTITIONERS. By I. HARRIS, M.D., L.R.C.P., Honorary Physician-in-Charge, Cardiographic Department, Liverpool Northern Hospital. Pp. 196; 50 illustrations. New York: William Wood & Co., 1922.

THE author's practical knowledge of cardiology is apparent to anyone reading this book, but his selective judgment is decidedly open to criticism. He accepts without question, for example, the Diplococcus and Streptococcus rheumaticus as the causes of rheumatic endocarditis, and suggests the use of a diplococcus vaccine. He also recommends vaccine treatment for acute septic endocarditis. In cardiac conditions other than the arrhythmias, too great stress is laid upon the diagnostic value of the electrocardiogram. On page 148 the reference to the hemolytic streptococcus as the cause of subacute endocarditis is evidently a mistake. Discrimination on the part of the reader is therefore required beyond what could be expected of the practitioner or student for whom this book was designed. A.

THE HISTORY OF MEDICINE. By WALTER LIBBY, M.A., Ph.D., University of Pittsburgh. Pp. 427; 9 illustrations. Boston and New York: Houghton Mifflin Company, 1922.

DOCTOR LIBBY has not attempted to make his book an encyclopedia of medicine, but on the contrary has devoted himself entirely to important epochs and periods and to the lives of the greatest of the medical scientists. In this way he has been able to sketch rather superficially the more important features of medicine. He has prepared a volume which makes very much more interesting reading than could be gotten from a book in which the narrative form is not employed. Furthermore, it is a book which should appeal not only to the physician but also to the laity, and can be recommended to anyone who is interested in medicine from the very general point of view, as well as to any individual who is interested in science as a whole. M.

MONTAIGNE AND MEDICINE. By JAMES SPOTTISWOODE TAYLOR, Commander, Medical Corps, U. S. Navy, M.D., F.A.C.S., Membre Société française d'histoire de la médecine. Pp. 244; 32 illustrations. New York: Paul B. Hoeber, 1922.

To a lover of Montaigne this delightful little book will be of great interest. To him who has delved deeply into Montaigne it will recall interesting excerpts from this charming author's works. To one who is not acquainted with Montaigne and his work Taylor's essays will open to him a delightful series of future pleasures. The book is well worth reading and would make a very agreeable remembrance to one's medical friends, as it is nicely bound and attractively gotten up. M.

"BRAIN ABSCESS:" ITS SURGICAL PATHOLOGY AND OPERATIVE TECHNIC. By WELLS P. EAGLETON, M.D., Medical Director, Newark Eye and Ear Infirmary, etc. Pp. 282; 46 illustrations. New York City: The Macmillan Company, 1922.

DR. EAGLETON has written an excellent book on brain abscess and one that fills a real need. In fact, it is not often that a book finds a more ready field of usefulness waiting for it than this book does. The author has taken great care in its preparation and has candidly set forth his own experience in this field, even though not by any means invariably encouraging, as well as a comprehensive review of the literature. No one has known a great deal about brain abscess, so this work will help anyone interested in the subject.

The reviewer is in entire accord with Dr. Eagleton when he states in the beginning that "in no other branch of surgery may the advisability of a major operation depend upon such apparently trivial manifestations; in no other part of the body will neglect of slight hemorrhage play so important a part in the recovery or in the future well being of the patient," etc. As a matter of fact, no one should be allowed, unless in dire emergency, to invade the cranial cavity for brain abscess or any other acute or chronic lesion of the brain who has not taken the trouble to develop a special technic, a large part of which is the proper handling of nerve tissue. It is unusual, therefore, for a specialist in another field, although an allied one, to develop this necessary point of view and technic as unquestionably Dr. Eagleton has done. There are a few little things about the book that the reviewer might have done differently. For instance, he would have changed the order and put Part III, Surgical Diagnosis, and the succeeding chapters up to Chapter XIV, Complications and Results, in the first part, as this seems a more logical sequence. A good deal of stress is laid on technic, perhaps rightly so, since acute brain abscess is an emergency and must be so dealt with

wherever it arises. The illustrations for the most part are good and amplify the text. The reviewer extends his congratulations to the author on a book, well done, which he believes is destined to become a classic in its field. R.

DISEASES OF WOMEN. By HARRY STURGEN CROSSEN, M.D., Clinical Professor of Gynecology, Washington University Medical School. Fifth edition. Pp. 1005; 934 engravings. St. Louis: C. V. Mosby Co., 1922.

WRITTEN for the general practitioner, this book describes in ample detail the methods to be used in determining a diagnosis and presents clearly the treatment to be selected and applied by him. The technical description of major operations is not within its scope, but the important features of preparatory and after-treatment are fully covered. The arrangement of the subject-matter has been accomplished with such evident skill that its value for easy reference is readily apparent. Where repetition has been necessary for this purpose it may be not only excused but commended. The liberal use of well selected and appropriately placed illustrations is noteworthy. This edition shows extensive revision and brings up to date the phases of gynecology in which the most recent advances have been made. The emphasis placed on pathology by the addition of new illustrations is in keeping with the character of the text. L.

CHLOROFORM ANESTHESIA. By A. GOODMAN LEVY, M.D., M.R.C.P., Physician to the City of London Hospital for Diseases of the Chest. Pp. 155; 9 illustrations. New York: William Wood & Co., 1922.

THE administration of chloroform is becoming a lost art in many hospitals in this country. The literature of the last few years has aroused a vague fear of its effects, so that, when it is occasionally selected because other anesthetics are strongly contraindicated, it is too often given timidly because the scientific basis of its dangers is not well understood. The author's experience as an anesthetist, his experimental work with animals, and his presentation of the basal sciences as well as the physiology concerned give a stamp of authority to the work that is convincing. The book places chloroform anesthesia on a newer and firmer basis. It commends itself not only to anesthetists but to others interested in the principles of the distribution of a drug in the tissues. L.

THE BASIS OF PSYCHIATRY. By ALBERT C. BUCKLEY, M.D., Medical Superintendent of Friend's Hospital, Frankford; Associate Professor of Psychiatry, Graduate School of Medicine, University of Pennsylvania. Pp. 447; 79 illustrations. Philadelphia and London: J. B. Lippincott Company.

IN this book, relatively small when one considers the subject, Dr. Buckley has placed a world of information regarding mental diseases. The first 115 pages of the book are given over to chapters on biologic phenomena, cerebral development and receptive apparatus, mental development, and psychological processes; in these pages is put forth a real foundation for any student of psychiatry. Dr. Buckley's discussion of the psychoses and psychoneuroses is clear, simple and easy to follow. The work is one of the best on psychiatry and the author should be congratulated on his effort.

W.

PATHOLOGY OF THE NERVOUS SYSTEM. By E. FARQUHAR BUZZARD, M.A., M.D., F.R.C.P., and J. GODWIN GREENFIELD, B.Sc., M.D., M.R.C.P., London. Pp. 334; 103 illustrations. New York: Paul B. Hoeber, 1922.

THIS is one of the few books devoted entirely to the pathology of the nervous system. It is well written, the paper and the illustrations are excellent, and the type clear-cut. From the standpoint of the neurologist it might be said that the book is somewhat elementary; but for students and those practitioners in lines other than neurology, this book will be an excellent guide to the changes brought about in the nervous system by disease. The first 304 pages are devoted to pathology; the remainder of the book takes up the various staining methods and the examination of the cerebrospinal fluid. The authors are apparently little acquainted with the writings of American neurologists, if one is to judge from the references.

W.

DISEASES OF THE THYROID GLAND. By ARTHUR E. HERTZLER, M.D., F.A.C.S., Professor of Medicine in the University of Kansas School of Medicine; Surgeon to the Halstead Hospital, Halstead, Kansas, etc. Pp. 245; 106 illustrations. St. Louis: C. V. Mosby Company, 1922.

IN calling attention to the advantages of the small country hospital for studying such conditions as goiter, which require prolonged observation, the author performs a real service. The present volume

is proof that such a study may be of distinct value. It is to be regretted however, that the presentation of statistics has been avoided. If, as the author states, statistics on goiter as now published are misleading in that they present the disease in too optimistic a light, it would seem that a valuable service might be performed by the country hospital in collecting statistics under the more favorable circumstances which may exist in such institutions, and in presenting the disease in its true light.

The first portions of the book are taken up with considerations of goiter which would appeal equally to the physician and the surgeon. The last two chapters are devoted to surgical considerations. The style is interesting, the illustrations good. The book contains points of practical value to the physician or the surgeon, and is decidedly worth reading. A.

SYPHILIS OF THE INNOCENT. By HARRY C. SOLOMON, M.D., Chief of Therapeutic Research, Boston Psychopathic Hospital; Instructor in Psychiatry and Neuropathology, Harvard Medical School, and MAIDA HERMAN SOLOMON, A.B., B.S., Research Social Worker, Boston Psychopathic Hospital, Boston. Pp. 239. Washington: United States Interdepartmental Social Hygiene Board, 1922.

THE authors, undoubted authorities upon the social and medical aspects of this disease, here present a study of the social effects of syphilis on the family and the community. To students of social hygiene this work will be of the greatest value, and in it the general practitioner and syphilologist will find a surprising amount of information condensed into a few very readable pages. A.

REGIONAL ANESTHESIA. By GASTON LABAT, M.D., Lecturer in Regional Anesthesia at New York University. Pp. 496; 315 original illustrations. Philadelphia and London: W. B. Saunders Company, 1922.

THE author states that "the object of this work is to afford the opportunity of acquiring rapidly a practical knowledge of regional anesthesia and to teach the reader how to use the method successfully," and he has fulfilled that object most abundantly. It is clearly and concisely written in such a way that a person can rapidly gain the desired information about a region of anatomy where he had never used regional anesthesia previously. The last chapter on the "relative value of regional anesthesia" might well have been given a first chapter position for the benefit of those who have had

doubt about, or no experience with, this form of anesthesia. The diagrammatic illustrations are most instructive as to points in technic and anatomy, and should familiarize one with structures instantly which might be otherwise disregarded.

It seems to the writer that this work would be a most useful addition to anyone claiming to do any type of surgery, for every region of the body is expertly covered, and it is known that regional anesthesia is most desirable in many cases and an absolute necessity in others. Any description of a work summarizing the amount of labor necessary to make it possible, and yet so thorough, so precise and so beneficial to both surgeon and the welfare of his patient, seems totally inadequate. B.

CLINICAL MEDICINE: TUESDAY CLINICS AT THE JOHNS HOPKINS HOSPITAL. By LEWELLYS F. BARKER, M.D., LL.D., Professor of Medicine, Emeritus, Johns Hopkins University; Visiting Physician to Johns Hopkins Hospital, Baltimore, Md. Pp. 617; 67 illustrations. Philadelphia and London: W. B. Saunders Company, 1922.

IT is difficult to estimate the worth of this book, for there is much in it to praise and much to criticize unfavorably. The thirty-one clinics are presented in the form of dialogue between Dr. Barker and one or more hyperstudents; each is a complete exposition of its special topic and displays the author's wide knowledge of clinical and laboratory medicine and of medical bibliography. The clinics, however, are unrelated and in many instances are concerned with rare or at least unusual diseases, for example: "Chronic progressive multiple ossifying myositis." It is difficult in this form of clinical presentation to avoid faulty emphasis, as, for example, occurs in the following sentence on page 186, where in speaking of the roentgen-ray plates it is pointed out that "the stomach is dilated and has not emptied itself at the end of fifteen hours; besides, the duodenal cap is not emptied."

Esoteric words and phrases abound—"the cardiovascular stripe," "smear of the gland punctate," "areflexia," "autoanthropophagus," for the latter of which the author almost apologizes.

As examples of bedside teaching these clinics are inspiring and suggestive to any one who studies the teaching of internal medicine, and this is true even though the careful editing which the clinics must have undergone has somewhat lessened their spontaneity. To Professor Barker's former students the book will certainly achieve its purpose, as stated in its preface, of recalling to them some of the interesting hours spent together. Inherently, however, the book can have but a limited usefulness for the average student or practitioner of medicine. P.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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Blood and Bone-marrow Findings During Life in Cryptogenetic Pernicious Anemia, Especially During the Stage of Remission.—I. ZADEK (*Ztschr. f. klin. Med.*, 1922, **95**, 66) has undertaken a study of the bone marrow during life, together with examinations of the blood, in pernicious anemia. From his comparative studies of the blood and marrow, he arrives at the following conclusions: the characteristic macrocytosis, anisocytosis and hyperchromia, with megaloblasts, observed at the height of an Addisonian anemia, is the expression of a blood regeneration resulting from increased blood destruction; with this, there is a megaloblastic reaction of the bone marrow of the long bones. Close relations exist between the degree of the megaloblastic reaction of the marrow and the number of erythroblasts and macrocytes circulating in the blood. The increased blood destruction may be followed clinically at this stage by the golden-yellow color of the serum with bilirubinemia, by urobilinuria and, at autopsy, by siderosis of the liver. The periods of improvement which occur in most cases of Addisonian anemia are usually *stages of relative remission*, which are related, both clinically and hematologically, to the symptom complex, pernicious anemia, since the hemolysis at this stage of the disease is only slightly decreased, with no, or only few, evidences of regeneration of the blood. During relative remissions, the marrow of the long bones likewise reverts to a more normal state, and in place of red marrow, one finds a yellow marrow, which again becomes red during a recurrence of the disease. The remission is not the result of the megaloblastic marrow reaction, since macrocytes and erythroblasts disappear from both blood and marrow. The megaloblastic marrow

is, therefore, not the primary lesion of the disease, but, rather, the reaction to the toxic, hemolytic poison of pernicious anemia. The examination of the marrow during life serves as an index of the severity of the disease as well as of its stage. In very few cases of Addisonian anemia is the improvement so great that no criteria of the disease are to be found hematologically. In these instances of *complete remission*, the red count and hemoglobin may be normal, though often the hemoglobin is somewhat reduced. Clinically, during such complete remissions, the only sequelæ of the anemia may be the myocardial insufficiency, achylia gastrica and spinal cord changes, which so often form a part of the clinical picture. The marrow of the long bones at this stage of the disease is meeting no unusual demands and is yellow fatty marrow devoid of erythroblasts. The megaloblastic bone marrow of pernicious anemia is one of the processes of the disease which is resolved during remissions. It is to be looked upon as a secondary, labile reaction, conditional—according to the individual resistance of the patient—upon the degree of increased hemolysis; and the degree of the megaloblastic marrow reaction is indicated by the cells in the blood. (Like most of his Teutonic confrères, Zadek is apparently content to remain in blissful ignorance of all work which emanates beyond the Rhine. Without intending to minimize the value of observations upon the marrow during life, it may not be amiss to point out the fact that the most important conclusions of Zadek were arrived at some twenty years ago by Warthin of the University of Michigan, whose results published in this *Journal*, were based upon autopsy findings at various stages of pernicious anemia.)

Reactions of the Cerebrospinal Fluid in Disseminated Sclerosis.—Ch. Achard and J. Thiers (*Compt. rend. Soc. de biol.*, Paris, 1922, **87**, 1006) report findings in the cerebrospinal fluid of disseminated sclerosis which may prove to be of diagnostic importance. In a case reported by Achard recently, a negative Wassermann reaction and a positive colloidal benzoin reaction (réaction du benzoin colloidal) were encountered. The latter test was reported: 122,202,222,000. Targowla and Muttermilch (*Ibid.*, 1922, **87**, 974) have recently reported similar changes in the spinal fluid in a patient ill with this disease. The authors report 2 further cases of disseminated sclerosis, in which the reactions of the cerebrospinal fluid were like those reported above. In a woman who died of the disease, they found a clear spinal fluid, which yielded a negative Wassermann test and a strongly positive colloidal benzoin reaction: 222,222,221,000. In the second patient, a man, whose spinal fluid was also clear and contained no cells, the Wassermann test was negative and the colloidal benzoin reaction was subpositive, in the sense that it gave a precipitate in the first two tubes, *i. e.*, in the syphilitic zone: 111,000,200,000. In this fluid A. Petit demonstrated the presence of spirochetes. If disseminated sclerosis is in reality a spirochetosis, as the researches of Petit seem to show, it would not be surprising, the authors point out, if some of the humoral reactions of another spirochetosis, syphilis, should be met with. One can thus explain a positive Wassermann reaction found at times in the cerebrospinal fluid of patients suffering from disseminated sclerosis, without necessarily concluding that the disease is syphilitic in nature.

THERAPEUTICS

UNDER THE CHARGE OF

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AND

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Intestinal Infections and Toxemias and Their Biological Treatment.—N. P. NORMAL and A. E. EGGSTON (*New York Med. Jour. and Med. Rec.*, 1922, **116**, 623) base their treatment on five factors: (1) The removal of foci of infection from the upper digestive and respiratory tracts; (2) the efficient non-surgical mechanical drainage of the colon; (3) sufficient doses of pure cultures of living strains of Bacillus acidophilus; (4) the maintenance of a protective intestinal flora by a proper diet; (5) autogenous vaccines in selected cases.

Phases of Gastrointestinal Infection, Pathology and Treatment.—G. R. SATTERLEE, (*New York Med. Jour. and Med. Rec.*, 1922, **116**, 619) states that chronic intestinal toxemia is a definite entity and is the primary cause of the protean symptoms characteristic of chronic intestinal disease. It may have one or more of the following sources: bacterial by-products of the food in the intestinal lumen; autogenous non-bacterial metabolic products arising from the digestive epithelium; local bacterial foci in the intestinal wall. Of these the last is by far the most important, as inferred from pathological findings and immunity studies. Successful treatment consists in the removal of all accessible foci of infection and the treatment of the bowel focus by antigens prepared from bacteria isolated from the mesenteric lymph glands at the time of operation or from the stools in those patients who have not been operated upon. If this treatment fails the radical operation of colectomy may in special cases be indicated.

The Effect of Magnesium Sulphate on the Secretion of Bile: Experimental Study.—E. B. FRAZIER (*Jour. Am. Med. Assn.*, 1922, **79**, 1594) undertook a series of experiments on dogs to determine whether magnesium sulphate introduced directly into the duodenum or injected intravenously caused any change in the amount or character of the bile secreted. In the control experiments the bile flow was found to be fairly uniform in fasting animals; and since all factors could be controlled, any fluctuation in the secretion could be ascribed to the injection of the salt. After intraduodenal injection, the duodenum, seen through the skin, contracted at first and then during the next thirty to sixty minutes remained in a state of wide relaxation. The initial contraction was probably due to the mechanical stimulation of the muscular wall by the needle. The effects on bile flow were entirely negative. Whether the magnesium sulphate solution

was injected directly into the duodenum or into the veins, the bile flow remained practically constant, though in a considerable proportion of experiments the secretion was lessened. When bile was injected into the duodenum there was a definite and prompt increase in the bile output confirming the generally accepted statement that bile itself is the best cholagogue.

The Effects of Thyroxin and Iodides on Metabolism.—F. HILDEBRANDT (*Therap. d. Gegen.*, 1922, **24**, 363) found that the feeding of thyroid extract to rats causes a loss of weight, an increase in O-consumption and a decrease in the respiratory quotient. Since there is no augmentation of urinary nitrogen, the decreased respiratory quotient is intrepreted as an indication of increased oxidation of fat. The intravenous injection of thyroxin causes identical changes in metabolism and the author agrees with Kendall in regarding thyroxin as the active principle of the thyroid gland. Thyroxin contains about 66 per cent of iodine and it occurred to the author that the alterations in metabolism might be due to the splitting off of free iodine; accordingly, the effects of iodine, in the form of potassium iodide and in amounts equivalent to that contained in thyroxin, were determined and were found to be the same as those following thyroid feeding or thyroxin injection. The intravenous injection of potassium iodide into rats fed on thyroid, stopped the loss of weight and flattened the gradient of O-consumption; in some cases there were gain in weight and decrease in oxygen intake. These experiments confirm the clinical findings that minimal doses of iodine lessen the metabolic upset of "hyperthyroidism." If large doses of potassium iodide are injected into thyroid fed rats, the loss of weight and the O-consumption are greatly exaggerated, a reaction that finds its counterpart in the distinctly harmful effects of large doses of iodides in "hyperthyroidism." Further experiments showed that the response to potassium iodide is not altered by thyroidectomy and the conclusion is drawn that the metabolic changes cannot be due to an action of potassium iodide on the cells of the thyroid glands. By a process of exclusion, the author is forced to conclude that the metabolic changes are due to a specific action of iodine on all the cells of the organism.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,
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The Vital Capacity of the Lungs of Children in Health and Disease.—STEWART (*Am. Jour. Dis. Child.*, 1922, **24**, 451) as a result of his exhaustive studies found that at either corresponding age, standing height, sitting height or body weight the vital capacity of the lungs is constantly greater with boys than with girls, the difference increasing with especial rapidity during the latter half of childhood. The curves

of vital capacity as plotted against age, standing and sitting height in general pursue a sinuous course showing a fairly uniform increase at first, followed later by a period of more rapid growth in lung capacity, which later diminishes in rate. The curve plotted against body weight for the boys showed a more uniform curve, while that for girls has a definitely convex form. The absolute annual increase in vital capacity in general is fairly uniform during early childhood, but increases in rapidity about the time of puberty and declines later. The relative increase in vital capacity apparently decreases at first, becomes relatively more rapid about the time of puberty and then proceeds at a slower rate again. The period of acceleration in the rate of growth in lung capacity begins and terminates at an earlier age in girls than in boys. Throughout childhood the vital capacity formed a greater proportion of the estimated adult maximum for women with the girls than with the boys. As a whole, as respects lung capacity at corresponding ages, the girls may be considered as relatively more mature than the boys. The vital capacity of the lungs apparently reaches a maximum near the twentieth year with the boys and probably slightly earlier with the girls. On using the proper values for the constant, the vital capacity may be computed accurately from the sitting height, the standing height, the age, or the body weight. The probable error of random sampling increases as the vital capacity increases, but all in all it is relatively small, amounting to less than 25 cc as a rule. Averages obtained from an infinitely large number of comparable series would vary only slightly from those obtained in the present limited series of this observer. The standard deviation or absolute variability increases as a rule as the vital capacity increases and is usually greater with boys than with girls of corresponding age and size. The coefficient of variation or relative variability for each sex decreases during the early years of childhood, increases about the age of puberty and later declines again. The extent of the dispersal of the individual observations from the averages, appears to be smaller when averaged in groups differing 5 cm. in standing height or 2 cm. in stem length, than when averaged according to age in years as estimated from the nearest birthday. Children may have a normal vital capacity even in the presence of a definite insufficiency of the mitral valves, and these individuals show little abnormal tendency to dyspnea on exertion. In more serious cases the vital capacity is greatly reduced, and the tendency to respiratory embarrassment is proportional to the reduction in lung capacity. When the condition of the heart improves the vital capacity gradually increases. Acute bronchitis produces a temporary reduction in vital capacity which in severe cases may be very marked. During the course of lobar pneumonia the vital capacity rapidly undergoes an enormous reduction even in cases free from pleurisy. The reduction is altogether out of proportion to the extent of the pneumonic process in the lungs. Following the crisis, the vital capacity gradually returns to normal in a comparatively short time. Physical signs of the disease may disappear before the normal capacity is reached. In complicated cases the return of vital capacity to normal may be greatly delayed. While bronchial asthma may cause an enormous reduction in the vital capacity immediately following an attack, the reduction promptly disappears as the symptoms subside. Even in children subject to the disease for several years there is apparently

no permanent reduction in the capacity of the lungs. With children showing slight evidence of tuberculosis such as a positive Pirquet reaction, and having a poor health record, and also with those having a definite tuberculosis the vital capacity is as a rule normal. In a few instances there is apparently some subnormal tendency of the lung capacity which leads to the suspicion of tuberculosis. In incipient pulmonary tuberculosis the vital capacity may be practically normal even in the presence of a very active and virulent infection in the lungs. In advanced pulmonary tuberculosis the vital capacity is reduced in proportion to the extent of the disease process. The abnormal tendency to dyspnea on exertion is much more marked where the reduced vital capacity is caused by disease of the heart than when caused by disease of the lung alone.

A Clinical and Chemical Study of Butter-soup Feeding in Infants. —BROWN, COURTNEY and MACLACHLAN (*Am. Jour. Dis. Child.*, 1922, **24**, 368) found that the use of butter-flour mixtures for very young and very small infants was generally attended by rapid gain in weight yet uniform, improvement in vigor, in tissue turgor, in disposition and in resistance to infection. Extraordinarily good results were obtained with many infants suffering from atrophy. It is not indicated, however, for children with diarrhea or other forms of fat or carbohydrate intolerance. The caloric intake with this form of food was usually high, averaging approximately 70 calories per pound. In some cases signs of mild rickets or of a condition simulating rickets, were seen after continuous use of butter-soup. No edema was encountered. If the weight became stationary after long use of butter-soup, the addition of protein to the food or temporary feeding with a cow's milk dilution, was sufficient to bring about a continuation of the rapid weight gain. The stools with this food were acid, strongly resembling those of breast feedings, but were much larger. Like breast milk feces they contained a high percentage of fat. There was generally a poor retention of fat, and sometimes a poor retention of nitrogen and of total salts especially by the older children. There was usually a fair retention of calcium. Sodium chloride was retained in abnormal amounts. The feces contained an excess of inorganic bases over inorganic acids, and the urine showed the reversed condition. The excess of bases in the feces was not to be accounted for by the quantity of fat excreted as soap, but apparently indicated the presence of lower acids.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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Drug Eruptions.—WILE, WRIGHT and SMITH (*Arch. of Dermat. and Syph.*, 1922, **6**, 529) in a preliminary study of iodide and bromide

exanthems report that iodide and bromide cannot be found in the purulent material from iodide and bromide acne. They state that cutaneous tests for sensitization to these drugs are invariably negative, so that it is impossible to use such tests to determine a preëxistent sensitiveness. WISE and PARKHURST (*Arch. Dermat. and Syph.*, 1922, **6**, 542) gave a valuable account of the eruptive phenomena associated with the administration of recent medicaments. They cite the observation of Stuhmer that seborrheic eruptions predispose to arsphenamine dermatitis, and that the eruption usually is most persistent at the sites of predilection for seborrhea. The arsphenamine "fixed exanthem," which has attracted much attention in the European literature, is a recurrent plaque of an urticarial or eczmatoid type which appears following each injection of the drug, tending to disappear between injections. The plaques may be solitary or as many as a dozen may appear. Pigmentation becomes marked at the site of the recurrent lesions. The resemblance to the antipyrin and phenolphthalein eruption is obvious. Lichenoid eruptions and actual outbreaks of lichen planus following upon courses of arsphenamine and mercury have been described. MC CAFFERTY (*Arch. Dermat. and Syph.*, 1922, **6**, 591) reports in detail a case of this type in which both the clinical and histological picture conformed to that of lichen planus. The familiar diffuse pigmentation of the skin and hyperkeratoses of the palms and soles which were long thought not to occur with the administration of the arsphenamines, are now known to be among the possible complications, and cases are cited from the literature as reported by Hoffmann, Heller, Philip and others. Herpetic eruptions are recognized as rather frequent after arsphenamine. There are no authentic reports of argyria following silver arsphenamine, according to these authors. The controversy as to whether an arsphenamine dermatitis can favorably influence the course of a syphilitic infection by arousing the defence mechanism of the skin ("esophylaxis" according to Hoffman) is reviewed. While there seems to be a weight of opinion in favor of the belief that an attack of exfoliative dermatitis favorably affects the course of a syphilitic infection, the effect may be only transitory, and too little time has elapsed for the collection of trustworthy figures. Barbital and medinal may give rise to erythematous eruptions suggesting the acute exanthemata and in some cases associated with red blotches, erosins and bullous lesions on the oral mucosæ. The blebs may appear from five minutes to several days after administration and may be confused with pemphigus and erythema multiforme. Itching plaques, generalized pruritus and urticaria have been seen after adalin and bromural. These eruptions may become eczematoid, or tuberose bromodermatous lesions may develop. Old people are especially susceptible. Phenobarbital produces scarlatiniform and rubeolar eruptions, dermatitis and urticaria. Oral lesions are frequent and may in the form of severe stomatitis and bullous lesions, with exfoliation of the mucosa, be the only manifestation of the idiosyncrasy. Cinchophen may produce angioneurotic edema, pyramidon may produce pruritus, swelling of the lip, erythema and purpura. Acetylsalicylic acid eruptions are fairly uniform, and consist of swelling of the face, chiefly the eyelids and lips within an hour, with involvement of the oral and nasal mucosæ. Intense general malaise and urticaria or

scarlatiniform erythema may develop. The palms may show a "dyshydrotic eczema." Hexamethylene may produce a burning and itching general eruption. Phenolphthalein eruptions have been previously described by Wise, and present characteristics similar to the antipyrin and fixed arsenical exanthems. The essential lesion is an urticarial plaque or patch which becomes edematous with each dose and subsides in the interim, leaving a residual pigmentation which by accumulation takes on a bluish or livid tinge and persists for months and even years after the ingestion of the drug is discontinued. The tendency to involve the genitalia gives rise to the so-called "blue penis." Erosions are frequent and may be mistaken for venereal lesions.

Effect of Treatment on Viability of Spirochæta Pallida.—RUBIN and SZENTKIRALYI (*Dermat. Wchnschr.*, January 28, 1922, p. 84) undertook to compare the efficiency of four methods of treating syphilis from the standpoint of their effect on the viability of the *Spirochæta pallida* after removal from the body. The purpose of the work was to check the results of Stejskal, who found that the length of life of spirochetes outside the body was shortened in inverse proportion to the time which had elapsed following a neosalvarsan injection, and that this drug caused the rapid disappearance of the organisms. With mercury on the other hand, he found that the essential fact responsible for the disappearance of the organisms was the healing of the lesion, and the drug as such had little effect upon the organisms themselves, but rather on the lesions. The authors further aimed to control the observation of Fantl regarding the resistance of spirochetes in a certain case to the treatment of the patient with inunctions and salvarsan, Fantl having suggested the possibility that the previous mercurialization had rendered the organisms more resistant to the subsequent use of arsphenamine. The series of early cases studied by the authors, 108 in number, were divided into four groups, the first treated only with mercury salicylate intramuscularly, the second with two injections of mercury salicylate followed by neoarsphenamine, the third by neoarsphenamine alone, and the fourth by the Linser mixture of neoarsphenamine and mercury bichloride intravenously. Their findings are of interest. The average life of the spirochete in the moist chamber when taken from untreated cases was twenty to thirty hours. On the other hand they found variations as high as one hundred and twenty-four hours. Living spirochetes were still demonstrable in the lesions of one case as late as twenty-seven days after the first injection of mercury salicylate, and following the sixth injection of the drug. There was a progressive decline in the viability of the organism as the lesion healed and as treatment was continued. They were not convinced that the mercurialization increased the viability or resistance of the organism in any of their cases, although in four they were resistant. In the second series they could elicit no evidence that the previous mercurialization had rendered the organisms resistant. In fact where specimens were taken with frequency, the gradual decline in their viability was apparent. It is of interest to note how small were the doses of neoarsphenamine (0.3 gm.) which caused complete disappearance of all organisms within twelve hours. The spirillicidal superiority of the arsphenamine was obvious. The authors were not impressed

with any superiority on this score in the combined injection of neosalvarsan and mercury bichloride. They were able to confirm the value of the preliminary administration of mercury in preventing the Herxheimer flare-up, but quote Lesser as not regarding this as an unmixed benefit in early cases, which he thinks need the "immunizing shock" of the acute reaction.

Non-specific Therapy of Syphilis with "Mirion." — Non-specific modes of therapeutic attack on syphilis have been engaging the attention of Continental authors. One phase of this discussion has centered around "Mirion," an organic synthetic (Benkö) containing an iodine radical, action of which is supposed to consist in the liberation of nascent iodine in contact with syphilitic lesions for its effect in provoking hyperemia securing a resolving local reaction, and a "mobilization" of the *Spirochæta pallida*. Frölich, Kyrle and Pfanner from Finger's Clinic employed 6000 injections of the drug in 400 cases and credit it with a provocative effect on the Wassermann reaction and the ability to produce a local or Herxheimer flare-up in syphilitic lesions. The iodine content of diseased tissue when this drug is administered is said to be much higher than that of healthy tissue. No spirillicidal qualities are claimed for "Mirion," its use being mainly that of an adjuvant to mercury and arsphenamine to assist in reaching inaccessible foci, much as in the case of iodides. The drug is given intramuscularly in doses of 5 cc but may be used intravenously. The worth of the new preparation is discussed by GAERTNER (*Dermat. Wchnschr.*, January 7, 1922, p. 14). No spirillicidal effects were demonstrable. Some evidence of a provocative effect on the Wassermann reaction was obtained. Urban from Török's Clinic, found in a smaller group of cases that no spirillicidal effect was obtained, that Herxheimer flare-ups were unusual, that early lesions did not respond at all to treatment with the drug and that no convincing provocative effect on the Wassermann could be obtained. Urban noted local flare-ups in trichophytosis under the drug. He feels that none of the effects obtained are markedly different from those obtainable in similar situations with foreign protein, and suggests that the 4 per cent gelatine in "Mirion" may be responsible for much of its action. KYRLE responds warmly (*Dermat. Wchnschr.*, March 18, 1922, p. 256), denying that he has overstated the possibilities of the preparation, and maintaining that the drug subserves its function as a stirrer-up of inaccessible foci and a non-specific therapeutic agent for syphilis.

Sodium Salicylate for Psoriasis.—BRAVO in a brief note (*Brit. Jour. Dermat.*, 1922, **34**, 353), reports favorable results from the use of Sack's method of treating psoriasis with intravenous injections of a 20 per cent sterile solution of sodium salicylate. (SACH'S original report is in the *Wien. klin. Wchnschr.*, April 21, 1921.) Sainz de Aja employs a 20 per cent solution giving $\frac{1}{2}$ gm. for the first dose and increasing $\frac{1}{2}$ gm. for each succeeding dose until 3 or 4 gm. are reached. The interval between injections is two or three days. No case reports or details are given.

OBSTETRICS

UNDER THE CHARGE OF

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The Prophylactic Rectification of Abnormal Positions.—BALLANTYNE (*Brit. Med. Jour.*, 1922, **2**, 845) states that, down to the close of 1921, the correction of malpositions and malpresentations in the antenatal department of the Edinburgh Royal Maternity Hospital was not satisfactory. Manipulation was tried and also postural treatment. A modified Trendelenburg was used in some cases with the hope that the presenting part would slip out of the pelvic brim and become movable above it, but this method was but little, if at all, successful. Since the beginning of 1922 a method described by BUIST (*Brit. Med. Jour.* 1921, **2**, 782) of using pads for this purpose has been employed, and the results for six months have been satisfactory. Of 509 pregnant women at the clinic, there were 26 cases where the occiput was posterior on the right side, 24 were rectified by pads, and the occiput made to assume anterior positions; the other 2 remained behind. In most of the cases the occiput moved anterior; the back remaining to the right; in some the usual left occipito-anterior position developed. One case was first diagnosed as left occipito-posterior and pads were applied, when it was found that the presentation was a breech, and external version produced a right occipito-anterior. It is thought that the use of pads changed the vertex to a breech presentation. The method as described by Buist is as follows: A binder is laid under the patient and two towel-pads are prepared. The first is rolled to about the thickness of a forearm, the second is folded to a flat pad six or seven inches square. The rolled pad is pinned to the binder in such a position that when the binder is firmly secured the pad will lie close in front of the anterior-superior iliac spine behind and parallel to the trunk. The flat pad is pinned so as to lie on the limbs, pressing them backward. It is sometimes useful to roll the patient to the side opposite the trunk and by hand bring the trunk so far as may be over to that side. The binder is then pulled firmly home. It has rarely been found necessary in the Edinburgh clinic to take the patient to a hospital to apply this method. The patient is asked to bring to the prenatal clinic a binder, two towels and safety pins. The pad and binder are then applied and the patient is allowed after a short rest to go to her home. She returns the next morning when the presenting part is usually found anterior. Occasionally the pads have to be applied again. The two failures are ascribed to the fact that the fetal head was so low in the mother's pelvis that by this method it could not be turned. In the 509 pregnant patients in six months there were 56 pelvic presentations. In 11 of these no attempt at version was made, as the pregnancy was not beyond the seventh month. In 14 cases cephalic version was accomplished by external manipulation, sometimes by one and occasionally by two

operators. In 7 chloroform was necessary, and success was obtained in 6 of these. In 3 other cases the attempt failed, because the amount of amniotic liquid was so small that the child could not be turned. In 19 cases spontaneous version occurred. In 2 the patient did not return to the clinic. In the 509, there were 3 cases of transverse presentation; in all of these, external manipulation was successful in securing cephalic presentation. The towel pads are advised in difficult breech and transverse positions.

Eclampsia and its Treatment and the Toxemia of Pregnancy.—Several of the papers upon these subjects recently were read before the British Congress of Obstetrics and Gynecology (*Jour. Obst. and Gynec. of the Brit. Emp.*, 1922, **29**, No. 3). EDEN comments upon the reports presented at the meeting of the Congress. Maternal mortality was computed in these reports from 2005 cases at 22.5 per cent. The infant mortality varied from 22 to 44 per cent. The percentage of surviving children varied from 44.4 per cent to 65.6 per cent. As regards the predisposing causes, primiparity was present in 69.3 per cent, multiparity in 30.7 per cent. The mortality is higher among multiparæ than among primiparæ. There is a distinct increase in cases of twin pregnancy, the liability to eclampsia being four or five times greater than a single pregnancy. In the great number of cases (84.7 per cent), there are premonitory symptoms which give warning. In 4 out of 5 cases an opportunity for preventive treatment was present if the significance of the premonitory symptoms was understood. There is an interesting difference in the severity of the disease in various portions of England, in the Midland districts the percentage of severe cases is somewhat higher than in other portions. Indications of danger are coma and pulse above 120; temperature above 103° F.; more than ten convulsions; the urine containing a large quantity of albumin; the absence of edema and the blood-pressure above 200 mm. When any two of these symptoms were present the case was thought to be severe. There was some difference in the results of statistics regarding the presence of edema and its results; this may be disregarded as a positive sign of danger. When methods of delivery are considered, the greater the interference, the higher was the mortality. Medical treatment passed through various periods prior to 1870, venesection, opium, ice pack, cold pack or cold baths, wet cupping in the loins and no obstetric interference was the treatment commonly employed. During the next twenty years narcotics and sweating were most used. Pilocarpin was given very freely and bleeding was abandoned. During this period in Germany maternal mortality was 33 per cent. From 1885 to 1890 the theory of toxemia became common and hepatic toxemia was recognized as a variety. Under early surgical operation in some of the German clinics the mortality fell to 18 per cent. In 1901 Stroganoff described his method which he originally intended should supplant active interference; this gave good results. The writer believes it to be unfortunate that there has been no concerted effort to distinguish between the results of various methods and to bring about an agreement in the use of those which gave the greatest promise of success. From his personal experience he believes that eclampsia and toxemia can usually be prevented, and

that prevention is of the most importance. The prophylactic treatment which he advises, consists essentially in confinement to bed and fluid diet only, mostly water, purgatives and diuretics. The case must be closely watched; observe the amount of urine, quantity of albumin and the blood-pressure. If the patient does not do well, or if relapses occur, the pregnancy must be terminated without regard to the interest of the child. The case should be under all circumstances a hospital case promptly, and he would have the patient sent to hospital after the first convulsion. On this, much can be gained by dividing the cases into "mild" and "severe;" so that proper methods of treatment for the two can be adopted and brought into general use. As little obstetric interference as possible should be employed. Simple medical treatment, carefully regulated and closely watched, gives the best results. The methods of the Rotunda Hospital in the treatment of eclampsia and its study are described by Fitz Gibbon. He believes that the toxemia is the primary complication, and that the division of cases under various heads is purely accidental from the development of one dominant symptom. He does not believe that an abnormal condition in pregnancy is the cause of toxemia. Were this so, the conditions found in the placenta would be practically uniform in these cases. So too would be the results in the fetus. In the early stages of the disease the fetus is well, and it is only when the toxemia is severe that the fetus suffers, and even in a large number of the severe cases the fetus is quite unaffected. The pathological findings in toxemia, eclampsia and toxemic hemorrhage are identical. There is a subacute nephritis with a variable degree of focal necrosis in the other organs, especially in the portal symptom of the liver. There is evidently a common irritant substance excreted by the kidneys, injuring their structure, and affecting the other tissues of the body. Two conditions commonly seen in pregnancy favor toxemia. One is the tendency to overeat and the other constipation. Pregnancy greatly increases the activity of the tissues in the body. This naturally throws an increased burden upon the organs of elimination, and where these are damaged before pregnancy occurs, toxemia early follows. In the greater number of toxemic patients they have gained in weight during pregnancy. This is the result of their taking an excessive quantity of food, until the time comes when the eliminative organs rapidly fail and toxemia and eclampsia develop. The writer had never seen personally, toxemia in a primipara who followed a careful hygienic course, has maintained regular action of the bowels with purgatives if needed, and who had avoided excess of eating. Where patients are seen in early toxemia they can be relieved of the symptoms and carried through a pregnancy without recurrence, by attention to diet and the action of the bowels. If the excretory organs are already damaged, the amount of damage is important. He would summarize the causes of toxemia as deficient elimination, excessive ingestion of food and constipation. In treating toxemia the patient is kept in bed, purged, enemata are given and purgatives are continued, 2 or 3 doses daily being administered. The patient must drink at least 6 pints of water in twenty-four hours. When the symptoms have greatly abated, the secretion of urine has increased, and there is a moderate quantity of albumin only, the patient is allowed

to take ½ pint of milk and the diet is very gradually increased without meat. If this goes well the patient is allowed to go to her home and to return to the dispensary for treatment. She must follow diet strictly and must secure at least two movements of the bowels daily by the use of purgatives. If the patient does not respond to treatment sufficiently to be tried on a diet, or if she grows worse in trying to follow the diet, or if at any time the child is found to be dead, labor is brought on. This was never done until the eighth day of treatment, and in all the series of cases, was done only 5 times. One toxemic case died, and it was the intention to interrupt the pregnancy three days before she delivered herself. The patient developed a very severe septic pharyngitis and delay was thought to be safer. The majority of cases with live infants were at term or reached term under treatment and came spontaneously into labor. When there is pronounced vomiting nothing is given by the mouth from twenty-four to forty-eight hours. Enemata are frequently administered, lavage of the colon, and a warm solution of bicarbonate of soda was given under the breasts. At the end of forty-eight hours purgatives can always be given by the mouth. In eclampsia, so soon as possible, the stomach is washed out with bicarbonate solution until the fluid returns clear. A saline mixture and about ¾ of a pint of bicarbonate solution are introduced and left in the stomach. A long rectal tube is passed and carried up into the colon. Its introduction may be difficult and may take as long as thirty minutes. The colon is then irrigated with soapy water until the fluid returns well colored with bowel contents. This may require three or four gallons of fluid. The irrigation is continued until the fluid returns clear, when bicarbonate solution is substituted for the soapy water. Saline and bicarbonate solution are then inserted in the colon through the tube. The process of cleansing the colon may require from 8 to 12 gallons in quantity and one and a half hours in time. This is repeated in five hours and again in five hours if the patient does not return to consciousness sufficiently to drink, or the bowels have not begun to act spontaneously. When the patient recovers consciousness the treatment for toxemia is followed. If labor comes on, delivery is completed when the presenting part reaches the perineum, unless the labor ends spontaneously in a short time. No other interference is practised; while the patient is wholly or partially unconscious she is kept lying on her side, so that fluid may run out of her mouth. If the patient is severely ill, 40 ounces of bicarbonate solution are given under the breasts. Large poultices are placed over the loins and maintained until there is a fair secretion of urine. In few cases did the quantity of morphine given exceed in all 0.5 grain. The writer is convinced that morphine does not control the fits, and that it delays elimination and has a tendency to produce respiratory failure. Under the methods described as above, the Rotunda Hospital in twenty years has treated 214 eclamptics with 19 deaths (8.87 per cent). This includes the death of any woman who suffered from eclampsia without regard to the actual cause or time of the death.

GYNECOLOGY

UNDER THE CHARGE OF

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Conservative Versus Radical Operation for Myoma.—The use of a intelligent follow-up system is becoming more and more apparent to intelligent surgeons throughout the world since it is only by means of some such system that we can have a clear understanding of the results of our treatment. For example, the question of the advisability of removing both appendages when operating for the cure of a fibroid uterus or a chronic metritis is one that has not yet been settled. Indeed it may never be, except by carefully analyzing the end-results in such cases, as has been done by our British colleague BRIDE (*Jour. Obstet. and Gynec. of the Brit. Emp.*, 1922, **29**, 68). By such methods we shall have some definite facts upon which to base our opinions, rather than by merely stating opinions *per se*. In his series of three hundred cases the most striking feature in comparing the results of the two procedures, *i. e.*, ovarian ablation or conservatism, is the fact that there is so little difference in the percentage of adverse symptoms after either type. One would expect to find the adverse symptoms of the artificial menopause very much more marked after the radical operation, and to find few, if any, after the conservative procedure. With regard to the flushings and the effect on the patient's sexual feelings, there is certainly a larger percentage suffering after the radical operation, and in a lesser degree the physical capabilities of patients seem better after the conservative than after the radical operation. In this investigation the general health was improved in a very large percentage of cases after either operation, but there was a distinct preponderance after the radical operation—91 to 84 per cent. The temperament of the patients after either operation does not seem to have been much affected, but a slightly higher percentage complained of irritability after the conservative than after the radical procedure in the proportion of 28 to 26 per cent. This again is slightly in favor of the radical operation. There is a greater frequency of flushings after the radical than after the conservative operation, although whichever procedure be adopted, a very large percentage of patients will suffer from flushings and sweats for a certain period of time; the less marked as a rule, the more the ovarian tissue that has been preserved. What is surprising is not that 91 per cent had flushes after the radical operation, but that 73 per cent had them after the conservative operation. Pain was noted more frequently after the conservative operation than after the radical in the proportion of 18 to 7 per cent, which seems to the writer to be one of the strongest pleas for the radical

operation. Information about the effect of the removal of both ovaries on the sexual relationships of patients is difficult to obtain, but this series shows that these are more disturbed when both ovaries are removed than when some ovarian tissue is left, nearly 40 per cent as compared with 27 per cent: 15 per cent of these radical cases suffered from dyspareunia, chiefly due to narrowing of the vagina from atrophic changes. Briefly summarizing, the author believes that so far as the majority of the manifestations of the artificial menopause are concerned, there is very little to choose between the two types of operation. The advantage lies with the radical operation in every way except the occurrence of flushes and the sexual disability, and the surgeon must decide whether the advantages of the radical operation outweigh these disadvantages, since the radical procedure is easier, quicker and therefore safer for the patient. Furthermore, the final result is better as there remains afterward a smoothly peritonized pelvic floor with a linear scar and there is less risk of the formation of adhesions. Most important of all, the possibility of the ovaries undergoing such pathologic changes as to render necessary a second operation for their removal is done away with.

Milk Therapy of Pelvic Infections.—GELLHORN (*Jour. Missouri State Med. Assn.*, 1922, **19**, 341) calls attention to the fact that from observations made in almost all fields of practical medicine the conclusion has been reached that protein substances, introduced "parenterally," that is, by subcutaneous, intramuscular or intravenous injection, have the faculty of stimulating the cells to greater activity. All cells of the body feel this rejuvenating influence, but none more so than those cells which have been weakened or paralyzed by infection. The protoplasm again develops phagocytic properties, the toxins are neutralized by a fresh production of antibodies and ferments, the local metabolism is intensified, and the pus is absorbed. Under favorable circumstances the infected organ or tissue may thus rid itself of its enemy and normal conditions may be reëstablished. It stands to reason that only those cells can take up the fight for existence with any prospect for success that have not yet hopelessly been damaged, and as a matter of fact, practical experience has shown that foreign protein therapy gives a promise of cure largely in subacute and early chronic cases of salpingitis and pyosalpinx and is apt to fail in cases of very long standing. While this struggle goes on beyond the reach of our eyes, yet there are indications and outward manifestations to the effect that these protein injections have made themselves felt. In most cases there are chills and fever soon after the injections, or there may be nausea or headache. This is the general reaction as distinguished from the local reaction which occurs in the affected part itself and consists of a transitory increase of local pain and occasionally a brief increase in the size of the inflammatory tumors. A number of proteins have been recommended and used to advantage, but the writer has confined his work to the use of milk. The technic is exceedingly simple. Five cubic centimeters of sterilized milk are injected into the gluteal musculature and the injections are repeated at intervals of from three to five days. The amount injected is gradually increased to 10 cc. The average number of injections in the writer's series was

eight, although 1 patient received as many as twelve. The injections are not painful and anaphylactic shock has not been observed. Of 10 cases of gonorrhea of the tubes, 6 were cured completely; of these, 2 had large tumors which disappeared entirely; 2 patients were improved and 2 patients were unimproved. Three other patients with rather rare pathologic conditions in the pelvis were cured or materially benefited by the milk injections. It appears that mainly the tubes, the uterus, and possibly the bladder, are favorably influenced by foreign protein therapy. The ovaries seem to remain refractory. Exudates are brought to absorption, but adhesions are left undisturbed. This report of the author is of interest both as a curiosity and as a new method of treatment. However, inasmuch as he states that the treatment is applicable mainly to recent inflammations of the tubes, which very frequently tend toward spontaneous resolution, the editor cannot help but look upon this new trick as perhaps another *post hoc ergo propter hoc.*

Ovarian Organotherapy.—In judging the results of ovarian therapy, most of us have unconsciously succumbed to the familiar "post hoc propter hoc" error, states NOVAK (*Endocrinology*, 1922, **6**, 599) who has made an intensive survey of the literature on the subject in recent times. He believes that if there is any field of medicine in which a healthy skepticism is urgently needed, it is that of endocrinology, and more particulary that of endocrine therapy. Incalculable harm has been done by the trashy superficiality, the ignorance, and, at times, the commercialism which are reflected in much of the enormous literature which has grown up, mushroom-like, within the past decade or so. Especially unfortunate has been the influence of several books published quite recently. We must resign ourselves to the fact that future progress in endocrinology, including, of course, organotherapy, will be a slow developmental process, as it has been in all other branches of medical science. It will mean a tedious search for truth on the part of many men from many lands. Each year will add a few nuggets of knowledge, and now and then a bigger find will spur all the searchers to renewed efforts. It cannot be said that there has been any noteworthy advance in ovarian therapy in the quarter century and more which has elapsed since its introduction. This is especially true as applied to the preparation of the commercial extracts upon which the profession as a whole is dependent. The stellar role in the future development of this branch of organotherapy will unquestionably be played by the biological chemist. The time will almost surely come when we shall be able to place in the patient's circulation the specific secretions of the ovary or corpus luteum, as we now can of the thyroid, and when we shall not be obliged to strain the imagination to see good results from ovarian therapy. The foregoing words of caution from Novak, while admittedly skeptical, are none the less of great value at the present time, happily being in marked contrast to the numerous overenthusiastic reports along this line, many of which are made by careless observers and cannot stand the glare of the scientific searchlight.

OPHTHALMOLOGY

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Clinical Significance of Dark Adaptation.—SCHINDLER (*Klin. Monatsbl. f. Augenh.*, June, 1922, p. 710), based upon personal research, substantiates in general Behr's claims as to the behavior of dark adaptation in various diseases of the optic nerve and the basal visual paths. Behr states that inflammatory and chronically degenerative processes markedly lower dark adaptation, whereas processes acting more mechanically upon the optic nerve and the basal visual path, such as tumors, hemorrhages, etc., either do not influence dark adaptation at all or only to a slight extent. Examination of the adaptation may assist in the early differential diagnosis between papillitis and choked disk; such examination may point to early neuritis where the differentiation between neuritis and pseudoneuritis is in question. It may suggest the prognosis in retrobulbar neuritis; it is also of value for the recognition of probable tabetic atrophy in that disturbance of dark adaptation is a constant symptom in this affection. In functional ocular complaints and sympathetic irritation the adaptation test is without value; its normal occurrence in eclampsia bespeaks congestive conditions at the nerve. As regards the value of the examination for clinical purposes, it is not absolutely necessary, not being indispensable either for diagnosis or for therapy; neither is it always reliable, as it demands much time and patience on the part of both physician and patient, and is so largely dependent upon the attention and intelligence of the latter. At the same time the test is of great value clinically in that it supplements the data otherwise determined and enlarges our knowledge of the physiology and pathology of vision.

Syphilis of the Orbit.—RAFFIN (*Klin. Monats. f. Augenhk*, May, 1921, p. 747) refers to the rarity of syphilis of the orbit, amounting in the statistics of Birch-Hirschfeld to but 0.013 per cent of all diseases of the eye. The affection frequently resembles the clinical picture of numerous other diseases of the orbit, especially tumor; for this reason, and from its rarity, its significance frequently remains unrecognized. The periosteum is almost invariably the primary seat of the affection, while the bone is involved only secondarily. The affection presents itself either as an exudative hyperplastic periostitis with thickening of the periosteum, or else as a gummous periostitis with circumscribed nodes of soft, gummous or firmer consistence. The hyperplastic inflammation occurs usually in the late secondary period, the gummous in the tertiary period. Clinically periostitis of the orbital margin

can be differentiated from disease of the deeper portion. Every variety of transition occurs between slight, hardly demonstrable thickening of the orbital margin and the formation of circumscribed nodes within the orbit. Three symptoms are of diagnostic importance: Severe cephalalgia with nocturnal aggravation, sensitiveness to pressure at the affected portion of the orbital wall, and, finally, the therapeutic test. The presence of other symptoms of lues is, of course, important; the Wassermann reaction is generally strongly positive.

Diabetic Retinitis.—ONFRAY (*Ann. d'Oculist*, August, 1922, p. 599) summarizes a study of diabetic retinitis with reference to life and vision. He concludes that nine-tenths of diabetics affected with retinitis show vascular hypertension and renal insufficiency, that in half of these patients the renal insufficiency is only just commencing. These patients may be divided into two classes by measuring the vascular tension and by study of the coefficient of urea elimination. Untreated, such cases are liable to a fatal issue in two or three years; subjected to a hypotensile regimen, they may survive five, six and even ten years. Although complete blindness is rare, the prognosis as to sight is grave in all.

PATHOLOGY AND BACTERIOLOGY

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Effect of Hemorrhage on Complement of Blood.—Although it is known that, after hemorrhage, the leukocytes begin to increase within ten minutes, followed by an increase in platelets, that the red cells are made up much more slowly and that the hemoglobin content is the last to return to normal, the relation between these changes and the complementing power of the blood have not been studied. Accordingly, ECKER and REES (*Jour. Infect. Dis.*, 1922, **31**, 361) conducted several experiments to ascertain the changes induced in the complement of the blood of guinea-pigs "by profound and multiple hemorrhages and subsequent blood regeneration and what, if any, were the relations of this change to changes in the cellular elements." By carefully controlling the hematological counts and titrations, before and after bleeding the animals, it was found that complement has a regular curve of decrease and regeneration following a single severe hemorrhage, whereas repeated bleedings, causing extreme degrees of anemia with subsequent recovery, did not alter the level of complement. The complement curve was unaffected by later dilution of the blood by the

body fluids. This complement curve did not run parallel to that of any of the cellular elements of the blood nor was there any evidence that any of these cells were a factor in the regeneration of complement. The initial decrease was due to dilution of the blood and was soon overcome and restored to normal by an influx of complement from an unknown source.

Experimental Measles by Inoculation of Monkeys, Guinea-pigs and Rabbits with a Green-producing Diplococcus.—Having described previously a small Gram-positive diplococcus which was isolated from the blood, eye, nose, throat and sputum of patients with measles, during the preëruptive and early eruptive stage of the disease, TUNNICLIFF (*Jour. Infect. Dis.*, 1922, **31**, 382) conducted several experiments on monkeys, guinea-pigs and rabbits, by inoculating these animals intravenously and intratracheally with washings of the nose and throat of patients with measles and with the green-producing diplococci isolated from the blood and respiratory passages of human measles, as well as with control bacteria. It was ascertained that monkeys, guinea-pigs and rabbits were susceptible to measles when the nasopharyngeal washings were introduced and that the same symptoms and lesions might be produced in these animals by the green-producing diplococci. Those rabbits which were inoculated successfully with washings of the diplococci showed no symptoms when reinoculated with fresh virus. The green-producing diplococci from the blood and lung of rabbits which were successfully inoculated with diplococci from measles, produced Koplik spots and exanthems when introduced into other rabbits. Berkefeld N-candle filtrates of the diplococcus cultures, as a rule, showed abundant growth, but old cultures containing large forms sometimes multiplied only after several days incubation or on subculture into a favorable medium. The authoress concludes that "while the experiments indicate that the reaction is due to the coccus itself, and not to a separate virus carried by it, on account of the same symptoms being produced by cultures as late as the seventh generation and the absence of the reaction in rabbits injected with other bacteria isolated from the same plate as the green-producing diplococci, it is possible that the diplococcus possesses the selective power of carrying the specific virus of measles."

Studies upon Experimental Measles. I. The Effects of the Virus of Measles upon the Guinea-pig—Since the demonstration of the virus of measles in the circulating blood by Hektoen and the evidence that the virus is a filter-passer by Goldberg and Anderson, Blake and Trask have added to and confirmed previous knowledge at a time when Sellards shook our confidence in the earlier experimental findings. More recently, DUVAL and D'AUNOY (*Jour. Exp. Med.*, 1922, **37**, 257) conducted various experiments to determine the transmissibility of measles virus from man to the guinea-pig, the possibility of propagation of the virus from guinea-pig to guinea-pig, the effect of such passage on virulence and the relative infectivity of blood obtained from the prodromal, preëruptive, eruptive, and convalescent stages of the human disease. The human blood was collected by syringe, defibrinated and injected into the circulation within fifteen or twenty

minutes by cardiopuncture in amounts of 1 or 2 cc. It was found that the guinea-pigs reacted specifically to the intracardiac inoculations of the defibrinated blood from human measles cases, there being a constant rise in temperature and coincident leukopenia after an incubation period of nine to twelve days. This reaction occurred with blood obtained during a period corresponding approximately to the eruptive stage. Those animals which reacted and recovered were not susceptible to reinoculation with measles blood if tested over periods of two weeks to three months after recovery. From the constancy of the reaction, the authors concluded that the virus could be propagated by passage from infected guinea-pig to normal guinea-pig, that such passage apparently increased virulence, death resulting from acute hemorrhagic nephritis, and that intercurrent or secondary infection played no part. Attempts to cultivate the virus were unsuccessful. Later, (*Jour. Exp. Med.*, 1922, **36**, 231) the same authors report observations following inoculation of defibrinated human blood from measles cases into the ear vein of rabbits. A specific reaction analogous in all essential features to that of the human infection was encountered in the experimental animals, which showed after an incubation period of from two to five days definite pyrexia, leukopenia and cutaneous manifestations, consisting of exanthemata and enanthemata, the latter closely resembling the Koplik spots seen in man. Repeated passage of the virus through rabbits seemed to increase its virulence. Here again, those animals, dying presumably as a result of the specific virus, showed grave nephritic changes. The pneumonia so frequently observed in fatal human cases of measles was not seen in the rabbit, a fact which the authors explain "purely on the basis of the destruction of normal defense barriers by the specific excitant of the infectious disease, and the lack of resistance to the ordinary pyogenic micro-organism." In a third communication, (*Jour. Exp. Med.*, 1922, **36**, 239), these investigators found that Berkefeld-N filtrates of washings of nasopharyngeal secretions obtained from cases of the human disease at the height of the cutaneous reaction, when injected directly into the trachea or vein of guinea-pigs or rabbits, occasioned a definite and constant reaction. This reaction was characterized "by a complex of objective and subjective signs which very closely resembled the manifestations in man of the acute infectious disease measles." The incubation period for guinea-pigs ranged from nine to fourteen days, while rabbits reacted in from two to seven days, on an average of four days. The reaction consisted, in rabbits, of enanthem, exanthem and fever and, in guinea-pigs, of fever, marked leukopenia and grave nephritis in fatal cases. In other words, the findings following intratracheal and intracirculatory injections of nasopharyngeal secretions secured from human cases of measles were very similar to those obtained when defibrinated blood from human measles cases was introduced into the blood stream of rabbits and guinea pigs.

Pathological Lesions Produced in the Kidney by Small Doses of Mercuric Chloride.—On intravenous injection of mercuric chloride in concentration as low as 0.002 mg. per kilogram of weight, MENTEN (*Jour. Med. Res.*, 1922, **43**, 315) obtained well developed pathological changes in the proximal convoluted tubules and the ascending limb

of the loop of Henle of rabbits' kidneys. These changes developed immediately following injection. Attention was called to the possibility of similar degenerative changes resulting from the intravenous use of therapeutic preparations of trivalent mercury.

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School Health Supervision Based Upon Age and Sex Incidence of Physical Defects.—BAKER (*Am. Jour. of Public Health*, 1922, **12**, 465) concludes as a result of his study that: (1) The most important physical examination to be made in the school life of the child is the one occurring at the time the child enters school for the first time. (2) In order to make the work of health supervision of school children effective, a complete physical examination of each child should be made before the eight to ten-year period. If this can be done with 100 per cent efficiency, combined with follow-up that is 100 per cent effective and 100 per cent of treatments obtained, it should not be necessary to make regular physical examinations after the eight to ten-year period, reliance being placed after that time upon the routine inspection of the children in the classroom. This routine inspection will permit the nurse, doctor or teacher to pick out the cases of physical defects that have been in any way overlooked during routine physical examinations or which have originated after the eight to ten-year period. (3) An annual test for defective vision is desirable. (4) Unless the amount of money appropriated for school medical inspection is large enough to allow a complete and thorough physical examination each school year, the officials in charge of such work are not justified in spending any money in having physical examinations made after the eight to ten-year period unless the full health needs of the children below that age period have been met. (5) A logical deduction that might be drawn from this study is that great emphasis should be placed hereafter upon the preschool age period as the time when physical defects should be prevented or corrected. (6) To sum up the matter, the study would seem to show that the expenditure of time and money to make annual physical examinations of school children is not warranted and seems to be unnecessary. Analysis of the age and sex incidence of physical defects in this study shows that proper and adequate physical examinations made in the early life of the school child—that is, before the eight to ten-year period—are essential, and if these are properly followed up and suitable treatment obtained, the appropriation for this work will be spent in the most

economical way, the child's health will be more thoroughly protected and future disease and the sequelæ of physical defects be more adequately guarded against then by any of the present methods of school health supervision.

Analysis of 123 Cases of Anthrax in the Pennsylvania Leather Industry.—SMYTH and BRICKER (*Jour. Ind. Hyg.*, 1922, **4**, 53) report 123 cases of anthrax connected with the tanning industry in the twelve years from 1910 to 1921, inclusive. They state this number represents almost 12 per cent of the directly exposed employees. The mortality among these 123 cases was over 21 per cent. In the five-year period, for which accurate statistics were obtained (1916–1920, inclusive), there was a yearly morbidity rate of almost 2 per cent of the directly exposed employees. The directly exposed employees include those handling raw stock and those soaking and lining this stock. Anthrax has been contracted from the handling of non-packer cattle hides from Texas, Mexico, China, India and South America, and from goat skins from many regions. Anthrax has been contracted from the handling of both dry and wet, salted hides and skins, and from both certified and uncertified stock, and anthrax bacilli have been isolated from both. The present practice of certification offers little or no protection to the tanner. The mortality of cases treated in hospitals has been considerably less than one-half that of unhospitalized cases. In Pennsylvania apparently the best results of treatment have been obtained by the injection of strong phenol solutions (25 to 50 per cent) locally around the area of the initial lesion, with or without excision of the lesion. The use of antianthrax serum with excision of the local lesion has also given excellent results and its use should not be discontinued. The authors advocate a continued intensive use of a reliable serum, subcutaneously or intravenously, combined with excision of the local lesion and the injection of concentrated phenol solution around the wound. Early diagnosis, prompt hospitalization, if possible, and absolute rest are essential for success in any form of treatment. Anthrax continues to be a decided menace to both the cattle-hide and goat-skin tanner, and will continue to be so until some method is developed whereby tanneries cease to receive anthrax-infested, raw stock. Seymour-Jones advocates for England the prohibition of the importation of any raw stock not previously converted to the wet salt state by means of his formic acid and mercuric chloride method. Whatever method may be finally adopted, the authors state, they feel very strongly that all undisinfected imported stock should be disinfected at one or more centrally located government disinfecting stations before being shipped to the tanners, as the English government is doing at present with wool and hair.

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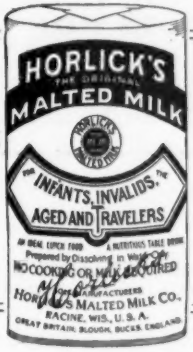

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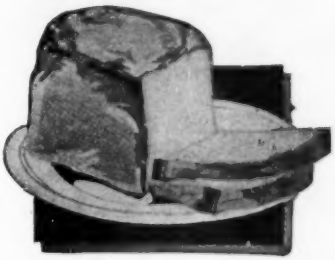

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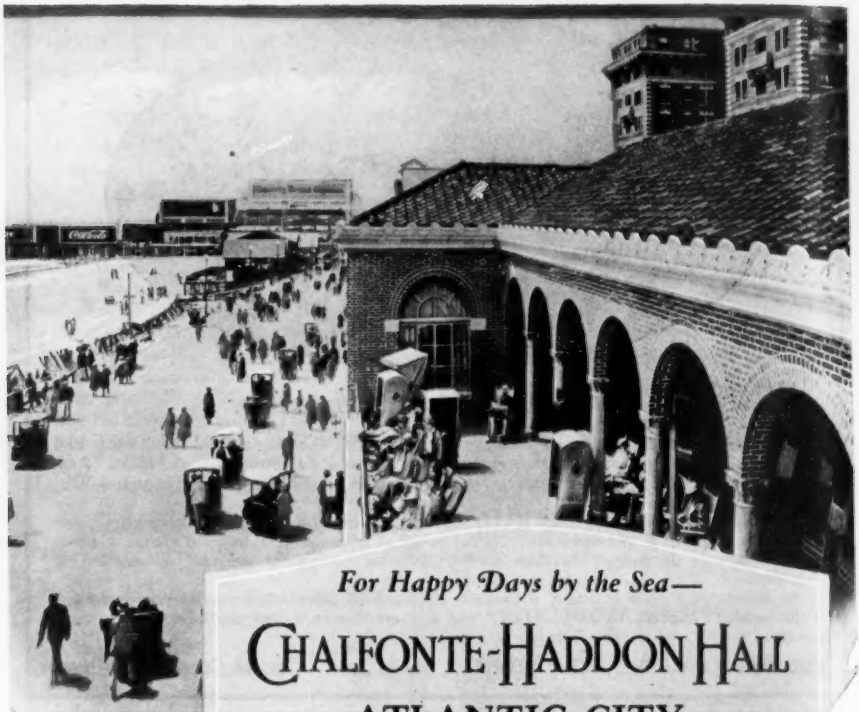

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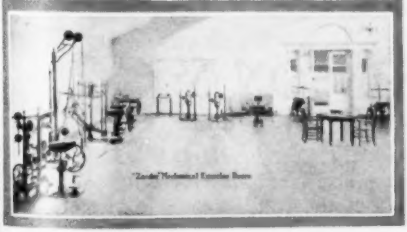

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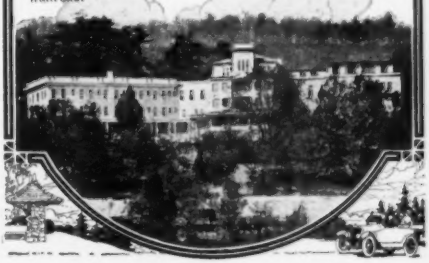

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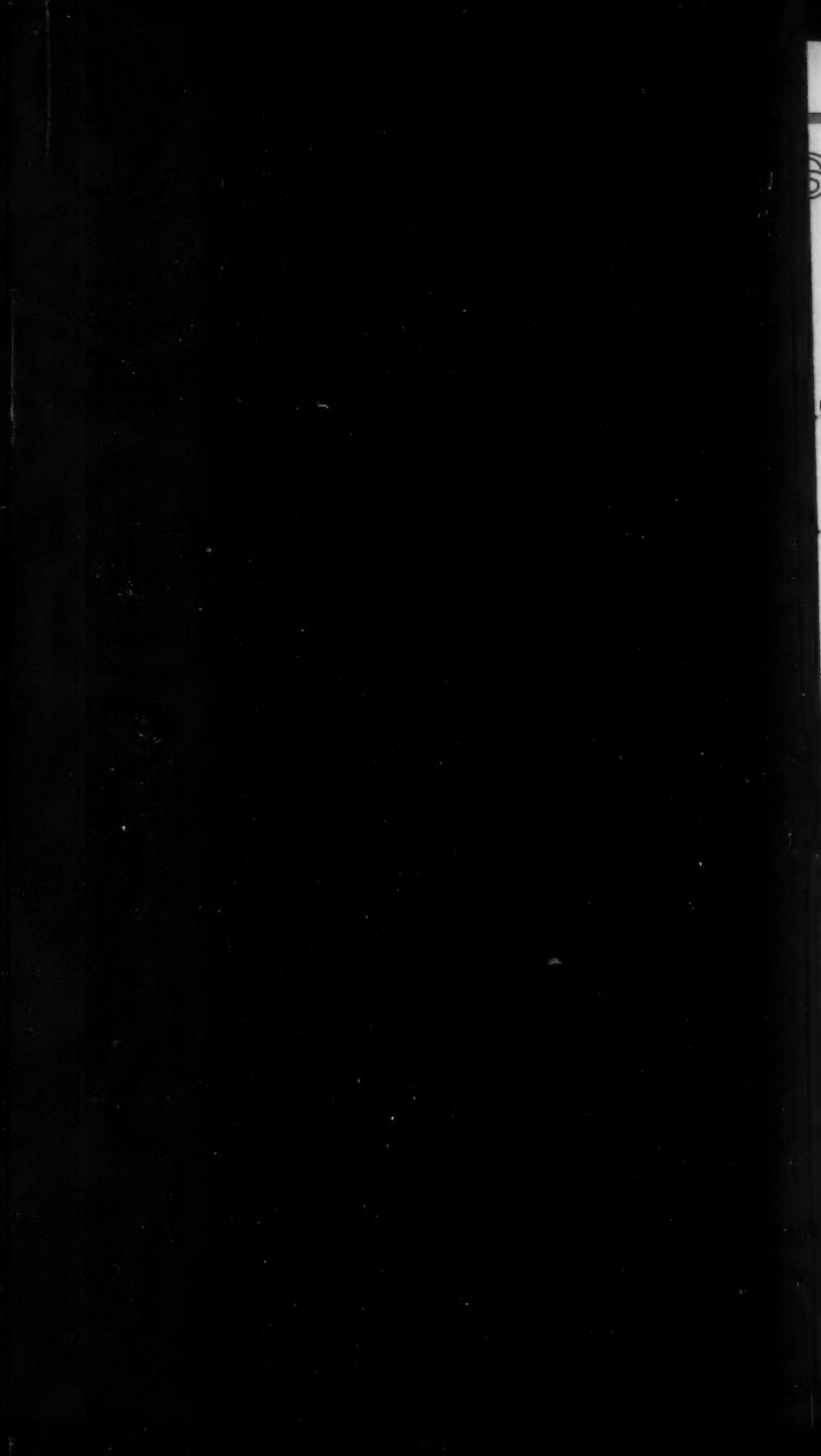
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